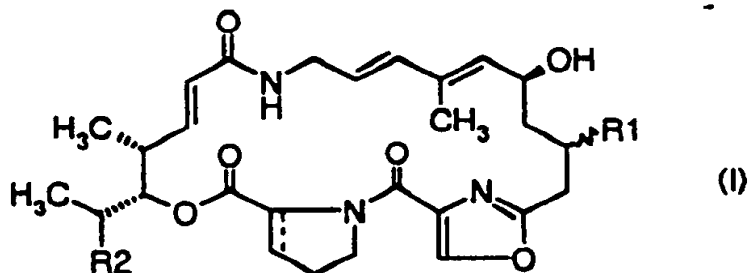


STREPTOGRAMIN DERIVATIVES, THEIR PREPARATION
AND COMPOSITIONS CONTAINING THEM

invent,

The present invention relates to group A streptogramin derivatives of general formula:



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in which

- R₁ is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl, benzyl or -OR''' radical, R''' being a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl or benzyl radical, or R'' represents -NR₃R₄, it being possible for R₃ and R₄ to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur,
- R₂ is a hydrogen atom or a methyl or ethyl radical, and

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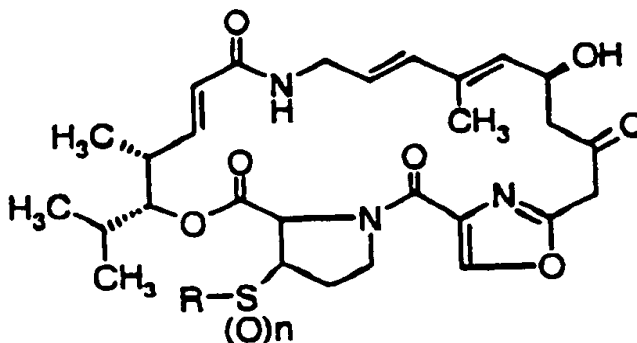
- the bond --- represents a single bond or a double bond,

as well as their salts, which exhibit a particularly
5 advantageous antibacterial activity and a good degree
of metabolic stability.


Among the known streptogramins, pristinamycin
(RP 7293), an antibacterial of natural origin produced
by *Streptomyces pristinaespiralis* was first isolated in
10 1955. The pristinamycin marketed under the name
Pyrostacine⁷ consists mainly of pristinamycin II_A
combined with pristinamycin I_A.

Another antibacterial of the class of
streptogramins: virginiamycin, has been prepared from
15 *Streptomyces virginiae*, ATCC 13161 [Antibiotics and
Chemotherapy, 5, 632 (1955)]. Virginiamycin
(Staphylomycine⁷) consists mainly of factor M₁ combined
with factor S.

Semisynthetic derivatives of streptogramins
20 of structure:

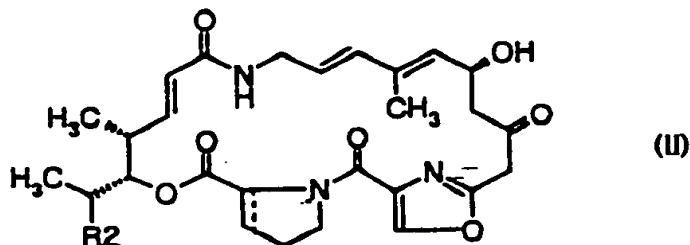


for which n is 0 to 2 have been described in patents EP 135410 and EP 191662. Combined with a semisynthetic component of group B streptogramins they manifest a synergistic action and can be used by the injection route.

In general formula (I), unless otherwise stated, the alkyl radicals are straight or branched and contain 1 to 6 carbon atoms; the cycloalkyl radicals contain 3 to 4 carbon atoms; the chain  at the 16-position means: when R'' is other than -OR''' or -NR₃R₄, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is -OR''' or -NR₃R₄, the R and S epimers and mixtures thereof.

When R'' is a radical -NR₃R₄ for which R₃ and R₄ form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle, the latter may be in particular azetidine, azolidine or imidazolyl.

The streptogramin derivatives of general formula (I) may be prepared from the components of the natural pristinamycin of general formula:



in which R₂ is as defined above, by the action of an

amine of general formula:



in which R'' is as defined above, followed by the action of an agent for reducing the intermediate enamine (or oxime) obtained, and then, when it is
 5 desired to obtain a streptogramin derivative of general formula (I) for which R' is a methyl radical, followed by a second reductive amination, by the action of formaldehyde or of a derivative generating formaldehyde
 10 in situ and the reduction of the intermediate enamine.

The action of the amine is generally carried out in an organic solvent such as an alcohol (for example methanol or ethanol), a chlorinated solvent (for example dichloromethane, dichloroethane or
 15 chloroform), a nitrile (for example acetonitrile), or pyridine, at a temperature of between 0 and 30°C, and optionally in the presence of a dehydrating agent such as, for example, magnesium sulphate, sodium sulphate or molecular sieves. Preferably, the procedure is carried
 20 out under an inert atmosphere (for example argon). It is also possible to cause the amine salt to react. Preferably, to prepare derivatives for which the bond --- represents a double bond, the procedure is carried out in an organic solvent such as a nitrile (for
 25 example acetonitrile) in the presence of an acid, such as an organic acid (for example acetic acid); in this case, the addition of a dehydrating agent is not necessary. When a streptogramin derivative of general

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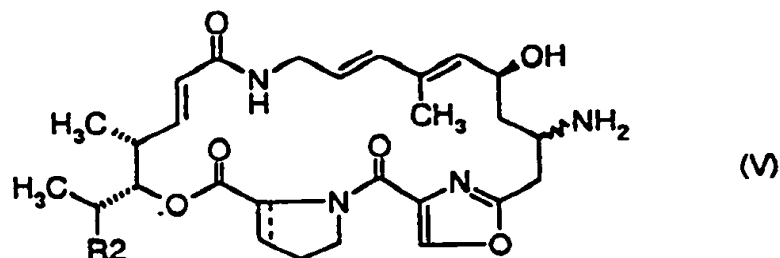


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According to the invention, the streptogramin derivatives of general formula (I) may also be prepared by the action of the ketone corresponding to the desired R'' radical on the amine-containing derivative

of general formula:



5 in which R₂ is as defined above, followed, when it is desired to obtain a streptogramin derivative of general formula (I) for which R' is a methyl radical, by a second reductive amination, by the action of formaldehyde or of a derivative generating formaldehyde
10 in situ and the reduction of the intermediate enamine.

The reaction is carried out under conditions similar to those described above.

The amine of general formula (I) may be prepared as described above, from a streptogramin
15 derivative of general formula (II).

The pristinamycin derivatives of general formula (II) correspond respectively to pristinamycin II_A (PII_A), to pristinamycin II_B (PII_B), to pristinamycin II_C (PII_C), to pristinamycin II_D (PII_D), to pristinamycin
20 II_F (PII_F), and to pristinamycin II_G (PII_G), which are known components of natural pristinamycin. The components PII_F and PII_G have been described in European patent application EP 614910.

Pristinamycin II_C (PII_C) and pristinamycin II_D

(PII_D) may be obtained as described by J.C. Barrière et al., Expert. Opin. Invest. Drugs, 3(2), 115-31 (1994).

The preparation and separation of the components of the natural group A streptogramins [streptogramins of general formula (II)] is carried out by fermentation and isolation of the constituents from the fermentation broth according to or by analogy with the method described by J. Preud'homme et al., Bull. Soc. Chim. Fr., vol. 2, 585 (1968).

Alternatively, the preparation of the natural components of group A may be carried out by specific fermentation, as described in patent application FR 2,689,518.

The streptogramin derivatives of general formula (I) may be purified, where appropriate, by physical methods such as crystallization or chromatography.

The derivatives of general formula (I) may in particular be obtained in the form of the 16R epimer. The separation of the 16R epimer form and the 16S epimer form may be carried out by flash chromatography, by high-performance liquid chromatography (HPLC) or by centrifugal partition chromatography (CPC), from the mixture of the 16R and 16S epimers.

The streptogramin derivatives of general formula (I) may be converted to the state of addition salts with acids, by known methods. It is understood that these salts are also included within the scope of

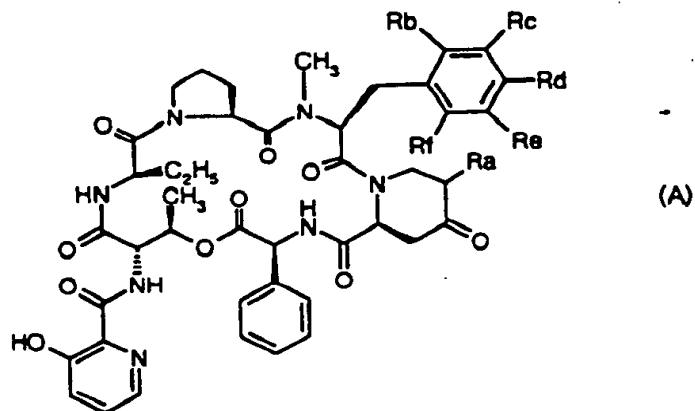
the present invention.

As examples of addition salts with pharmaceutically acceptable acids, there may be mentioned the salts formed with inorganic acids (hydrochlorides, hydrobromides, sulphates, nitrates, sulphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulphonates, ethanesulphonates, phenylsulphonates, p-toluenesulphonates, isethionates, naphthylsulphonates or camphorsulphonates, or with the substitution derivatives of these compounds).

The streptogramin derivatives according to the present invention have antibacterial properties and properties synergizing the antibacterial activity of the group B streptogramin derivatives. They are particularly advantageous because of their activity, alone or combined, as well as because of their enhanced metabolic stability compared with the previously known group A derivatives.

When they are combined with a component or a derivative of the group B streptogramins, they may be chosen, depending on whether it is desired to obtain an orally or parenterally administrable form, from the natural components: pristinamycin I_A, pristinamycin I_B, pristinamycin I_C, pristinamycin I_D, pristinamycin I_E, pristinamycin I_F, pristinamycin I_G, virginiamycin S₁, S₃ or S₄, vernamycin B or C, etamycin or from the semisynthetic derivatives as described in patents or

patent applications US 4,618,599, US 4,798,827,
US 5,326,782, EP 772630 or EP 770132, in particular the
streptogramin derivatives of general formula:



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in which,

1. Rb, Rc, Re and Rf are hydrogen atoms, Rd is a hydrogen atom or a dimethylamino radical, and Ra is a radical of structure $-\text{CH}_2\text{R}'\text{a}$ for which R'a is 3-pyrrolidinylthio or 3- or 4-piperidylthio which may be substituted with alkyl, or alkylthio substituted with 1 or 2 hydroxysulphonyl, alkylamino, dialkylamino (itself optionally substituted with mercapto or dialkylamino), or substituted with 1 or 2 optionally substituted piperazine rings, morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or 3-pyrrolidinyl (which may be substituted with alkyl), or alternatively Ra is a radical of structure $=\text{CHR}'\text{a}$ for which R'a is 3-pyrrolidinylamino, 3- or 4-piperidylamino,

- 3-pyrrolidinyloxy, 3- or 4-piperidyloxy,
 3-pyrrolidinylthio, 3- or 4-piperidylthio which
 may be substituted with alkyl, or R'a is
 alkylamino, alkyloxy or alkylthio substituted with
 1 or 2 hydroxysulphonyl, alkylamino, dialkylamino
 (itself optionally substituted with dialkylamino),
 or with trialkylammonio, 4- or 5-imidazolyl, or
 with 1 or 2 optionally substituted piperazine
 rings, morpholino, thiomorpholino, piperidino,
 1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or
 3-pyrrolidinyl (which may be substituted with
 alkyl), or
 Ra is a 3- or 4-quinuclidinylthiomethyl radical,
 or alternatively
2. Ra is a hydrogen atom and
- a) either Rb, Re and Rf are hydrogen atoms, Rd is a
 radical -NHCH_3 or $\text{-N(CH}_3)_2$ and Rc is a chlorine or
 bromine atom, or represents an alkenyl radical
 containing 3 to 5 carbon atoms [if Rd is $\text{-N(CH}_3)_2$],
- b) or Rb, Rd, Re and Rf represent a hydrogen atom and
 Rc is a halogen, or an aminomonoalkyl,
 aminodialkyl, alkyloxy, trifluoromethoxy,
 thioalkyl, C_1 to C_3 alkyl or trihalomethyl radical,
- c) or Rb, Rc, Re and Rf represent a hydrogen atom and
 Rd is a halogen, or an ethylamino, diethylamino or

methylethylamino, alkyloxy or trifluoromethyloxy, thioalkyl, C₁ to C₆ alkyl, aryl or trihalomethyl radical,

- 5 d) or Rb, Re and Rf represent a hydrogen atom and Rc is halogen or an aminomonoalkyl or aminodialkyl, alkyloxy or trifluoromethyloxy, thioalkyl or C₁ to C₃ alkyl radical, and Rd is halogen or an amino, aminomonoalkyl or aminodialkyl, alkyloxy or
 10 trifluoromethyloxy, thioalkyl, C₁ to C₆ alkyl or trihalomethyl radical,
- e) or Rc, Re and Rf represent a hydrogen atom and Rb and Rd represent a methyl radical.

15


It is understood that the combinations of the derivatives according to the invention and of the group B streptogramins are also included within the scope of the present invention.


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In vivo, on experimental infections of mice with *Staphylococcus aureus* IP 8203 at doses of between 25 and 150 mg/kg orally and/or subcutaneously (CD₅₀), they synergize the antimicrobial activity of pristinamycin I_B of prostinamycin I_A or of quinupristin
 25 (30/70 combination).

Finally, the products according to the invention are particularly advantageous because of their low toxicity. None of the products exhibited

toxicity at doses of 300 mg/kg or greater than 300 mg/kg by the subcutaneous route.

Of particular interest are the products of general formula (I) for which R_1 is a radical $-NR'R''$ for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl, cycloalkyl, allyl, propynyl, benzyl or $-OR'''$ radical, R''' being an alkyl radical containing 1 to 6 carbon atoms, an allyl or propynyl radical, or R'' represents $-NR_3R_4$, it being possible for R_3 and R_4 to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur, R_2 is a hydrogen atom or a methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts and in which the chain  at the 16-position means: when R'' is other than $-OR'''$ or $-NR_3R_4$, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is $-OR'''$ or $-NR_3R_4$, the R and S epimers and mixtures thereof; and among these products, most particularly the derivatives of general formula (I) for which R_1 is a radical $-NR'R''$ for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, a cycloalkyl, allyl, propynyl, benzyl or $-OR'''$ radical, R''' being an alkyl radical containing 1 to 3 carbon

atoms, or an allyl or propynyl radical, or R'' represents $-NR_3R_4$, it being possible for R_3 and R_4 to form together with the nitrogen atom to which they are attached a 5-membered saturated heterocycle, R_2 is a methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts and in which the chain  at the 16-position is as defined above.

More especially, among these products, the following derivatives are of great interest:

- (16R)-16-dimethylamino-16-deoxopristinamycin II_A;
- (16R)-16-methoxyamino-16-deoxopristinamycin II_B;
- (16R)-16-ethoxyamino-16-deoxopristinamycin II_B;
- (16R)-16-allyloxyamino-16-deoxopristinamycin II_B;
- 15 • (16R)-16-methoxyamino-16-deoxopristinamycin II_A.

The following examples, given with no limitation being applied, illustrate the present invention.

In the examples which follow, the 16-deoxopristinamycin II_A (or II_B) nomenclature means the replacement of the ketone function at the 16-position with 2 hydrogen atoms.

Example 1

(16R)-16-Benzylamino-16-deoxopristinamycin II_B

25 3 g of magnesium sulphate and 0.328 cm³ of benzylamine are added at about 20°C, under an argon atmosphere, to 1.06 g of pristinamycin II_B in solution in 15 cm³ of methanol. After stirring for 24 hours,

0.151 g of sodium cyanoborohydride and 0.5 cm³ of acetic acid are added. The reaction mixture is stirred for 1 hour and then filtered on Celite. The Celite is washed with 100 cm³ of methanol, the filtrate is concentrated under reduced pressure (2.7 kPa) to give a residue which is diluted in 200 cm³ of dichloromethane. The organic phase is washed with twice 100 cm³ of a 5% aqueous sodium hydrogen carbonate solution. The organic phase is decanted off and the aqueous phase is taken up in twice 50 cm³ of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give 1.3 g of a residue which is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (84-8-8 by volume)]. 0.424 g of a mixture of the (16R)/(16S) isomers = 65/35 of 16-benzylamino-16-deoxopristinamycin II_B, in the form of a yellow powder, and 0.144 g of the mixture of the (16R)/(16S) isomers > 95/5 of 16-benzylamino-16-deoxopristinamycin II_B, in the form of a yellow powder, are thus obtained. Each of these mixtures is purified by HPLC [C18 column (15-20 µm), (λ = 254 nm), eluent: acetonitrile-water (80-20 by volume)] to give, in total, 0.250 g of (16R)-16-benzylamino-16-deoxopristinamycin II_B in the form of a pale yellow powder melting at around 130EC (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and

1.00 (2 d, $J = 6.5$ Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.08 (d, $J = 6.5$ Hz, 3H : CH₃ at position 32) ; 1.43 (mt, 1H : 1H of CH₂ at position 15) ; 1.68 (s, 3H : CH₃ at position 33) ; from 1.70 to 2.00 (mt, 5H : 1H of CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 2.12 (mt, 1H : 1H of CH₂ at position 26) ; from 2.65 to 2.80 (mt, 1H : CH at position 4) ; 2.78 and 3.18 (2 dd, respectively $J = 16$ and 8 Hz and $J = 16$ and 4 Hz, 1H each : CH₂ at position 17) ; 3.25 (mt, 1H : CH at position 16) ; 3.47 (mt, 1H : 1H of CH₂ at position 9) ; 3.80 (mt, 1H : 1H of CH₂ at position 24) ; 3.81 and 4.02 (2 d, $J = 14$ Hz, 1H each : CH₂N) ; 3.96 (mt, 1H : 1H of CH₂ at position 24) ; 4.38 (mt, 1H : 1H of CH₂ at position 9) ; 4.66 (mt, 1H : CH at position 14) ; from 4.70 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 5.36 (d, $J = 9$ Hz, 1H : CH at position 13) ; 5.64 (mt, 1H : CH at position 10) ; 5.78 (dd, $J = 16$ and 2 Hz, 1H : CH at position 6) ; 6.00 (mt, 1H : CONH) ; 6.14 (d, $J = 16$ Hz, 1H : CH at position 11) ; 6.50 (dd, $J = 16$ and 5 Hz, 1H : CH at position 5) ; from 7.25 to 7.40 (mt, 5H ; aromatic H of benzyl) ; 8.09 (s, 1H : CH at position 20).

Example 2

25 (16R)-16-Cyclopropylamino-16-deoxopristinamycin II_B

9 g of magnesium sulphate and 0.6 cm³ of cyclopropylamine are added at about 20EC, under an argon atmosphere, to 3 g of pristinamycin II_B in

solution in 30 cm³ of methanol. After stirring for 17 hours 30 minutes, 0.43 g of sodium cyanoborohydride is added and then, after 30 minutes, 0.5 cm³ of acetic acid. The reaction mixture is stirred for 2 hours and then filtered on Celite. The Celite is washed with methanol and then the filtrate is concentrated under reduced pressure (2.7 kPa) to give 4.64 g of a yellow foam which is dissolved in 100 cm³ of ethyl acetate and 5 cm³ of methanol and then washed with 3 times 25 cm³ of distilled water. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2.7 kPa) to give 2.2 g of a yellow foam which is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (84-8-8 by volume)]. 0.61 g of a yellow powder is isolated which is stirred in 15 cm³ of ethyl ether, filtered and then dried under reduced pressure (2.7 kPa), at 30EC, to give 0.508 g of (16R)-16-cyclopropylamino-16-deoxopristinamycin II_B in the form of a cream-coloured powder melting at around 135EC (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.35 to 0.60 (mt, 4H : CH₂ of cyclopropyl) ; 0.97 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.33 (mt, 1H : 1H of CH₂ at position 15) ; from 1.70 to 2.00 (mt, 5H : 1H of CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at

position 29); 1.77 (s, 3H : CH₃ at position 33) ; 2.13 (mt, 1H : 1H of CH₂ at position 26) ; 2.29 (mt, 1H : CH of cyclopropyl) ; 2.74 (mt, 1H : CH at position 4) ; 2.82 and 3.25 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH₂ at position 17) ; 3.33 (mt, 1H : CH at position 16) ; 3.51 (mt, 1H : 1H of CH₂ at position 9) ; 3.83 and 3.99 (2 mts, 1H each : CH₂ at position 24) ; 4.35 (mt, 1H : 1H of CH₂ at position 9) ; 4.65 (mt, 1H : CH at position 14) ; from 4.70 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 5.39 (d, J = 9 Hz, 1H : CH at position 13) ; 5.65 (mt, 1H : CH at position 10) ; 5.79 (dd, J = 17 and 2 Hz, 1H : CH at position 6) ; 5.97 (mt, 1H : CONH) ; 6.17 (d, J = 16 Hz, 1H : CH at position 11) ; 6.53 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.12 (s, 1H : CH at position 20).

Example 3

(16R)-16-Allylamino-16-deoxopristinamycin II_B

By carrying out the procedure in a manner similar to that described in Example 1, but starting with 5 g of pristinamycin II_B in solution in 70 cm³ of methanol, 15 g of magnesium sulphate and 1.45 cm³ of allylamine and after adding at 24 hours [lacuna] 0.714 g of sodium cyanoborohydride and 5 cm³ of acetic acid, a solid is obtained after stirring for a further 1 hour and after treatment, which solid is purified by flash chromatography [eluent: dichloromethane-methanol (95-5 by volume)] to give 0.975 g of (16R)-16-allylamino-16-

deoxopristinamycin II_B in the form of a pale yellow powder melting at around 122-124EC.

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.96 and
 5 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and
 CH₃ at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at
 position 32) ; 1.38 (mt, 1H : 1H of CH₂ at position
 15) ; from 1.65 to 2.00 (mt, 5H : 1H of CH₂ at position
 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and
 10 CH at position 29) ; 1.77 (s, 3H : CH₃ at position 33) ;
 2.12 (mt, 1H : 1H of CH₂ at position 26) ; from 2.70 to
 2.80 (mt, 1H : CH at position 4) ; 2.74 and 3.13 (2 dd,
 respectively J = 16 and 8 Hz and J = 16 and 5 Hz, 1H
 each : CH₂ at position 17); from 3.20 to 3.35 (mt, 2H :
 15 CH at position 16 and 1H of CH₂N) ; from 3.45 to 3.55
 (mt, 2H : 1H of CH₂ at position 9 and 1H of CH₂N) ; 3.83
 and 3.98 (2 mts, 1H each : CH₂ at position 24) ; 4.38
 (mt, 1H : 1H of CH₂ at position 9) ; 4.70 (mt, 1H : CH
 at position 14); from 4.65 to 4.80 (mt, 2H : CH at
 20 position 3 and CH at position 27) ; 5.15 and 5.24 (2
 dd, respectively J = 10 and 1.5 Hz and J = 18 and 1.5
 Hz, 1H each : =CH₂ of allyl) ; 5.40 (d, J = 9 Hz, 1H :
 CH at position 13); 5.66 (mt, 1H : CH at position 10) ;
 5.80 (dd, J = 17 and 2.5 Hz, 1H : CH at position 6) ;
 25 from 5.85 to 6.00 (mt, 2H : CH= of allyl and CONH) ;
 6.16 (d, J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd,
 J = 17 and 5 Hz, 1H : CH at position 5) ; 8.10 (s, 1H :
 CH at position 20).

Example 4

(16R)-16-Propyn-2-ylamino-16-deoxopristinamycin II_B

By carrying out the procedure in a manner similar to that described in Example 1, but starting
5 with 5 g of pristinamycin II_B in solution in 70 cm³ of methanol, 10 g of magnesium sulphate and 1.3 cm³ of propargylamine and after adding at 22 hours [lacuna] 0.714 g of sodium cyanoborohydride and 5 cm³ of acetic acid, 5.5 g of a solid are obtained after stirring for
10 a further 3 hours 30 min and after treatment, which solid is purified by flash chromatography [eluent: dichloromethane-methanol (96-4 by volume)] to [lacuna] 0.266 g of (16R)-16-propyn-2-ylamino-16-deoxopristinamycin II_B in the form of an ochre-coloured
15 powder melting at around 124EC (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH₃ at
20 position 32) ; 1.53 (mt, 1H : 1H of CH₂ at position 15) ; from 1.60 to 2.00 (mt, 5H : 1H of CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.79 (s, 3H : CH₃ at position 33) ; 2.13 (mt, 1H : 1H of CH₂ at position 26) ; 2.26 (t, J =
25 2 Hz, 1H : CH propynyl); from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.76 and 3.16 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH₂ at position 17); 3.36 (mt, 1H : CH at position 16) ; 3.48

(mt, 1H : 1H of CH₂ at position 9) ; 3.56 (limiting AB, 2H : NCH₂ propynyl) ; 3.84 and 3.99 (2 mts, 1H each : CH₂ at position 24) ; 4.40 (mt, 1H : 1H of CH₂ at position 9) ; from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and CH at position 27) ; 5.36 (d, J = 9 Hz, 1H : CH at position 13); 5.69 (mt, 1H : CH at position 10) ; 5.80 (dd, J = 16 and 2 Hz, 1H : CH at position 6) ; 6.11 (mt, 1H : CONH) ; 6.17 (d, J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd, J = 16 and 5 Hz, 1H : CH at position 5) ; 8.08 (s, 1H : CH at position 20).

Example 5

(16R)-16-[(R)-sec-Butylamino]-16-deoxopristinamycin II_B

By carrying out the procedure in a manner similar to that described in Example 1, but starting with 5 g of pristinamycin II_B in solution in 70 cm³ of methanol, 10 g of magnesium sulphate and 1.92 cm³ of (R)-sec-butylamine and after adding at 20 hours of stirring 0.714 g of sodium cyanoborohydride and 5 cm³ of acetic acid, 5.6 g of a solid are obtained after stirring for a further 2 hours 30 min and after treatment, which solid is purified by flash chromatography [eluent: dichloromethane-methanol (96-4 by volume)] to give 0.680 g of (16R)-16-[(R)-sec-butylamino]-16-deoxopristinamycin II_B in the form of a yellow powder melting at around 156°C (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.90 to

1.15 (mt, 15H : CH₃ at position 30 - CH₃ at position 31 - CH₃ at position 32 and 2 CH₃ of (N-2-butyl)) ; 1.28 (mt, 2H : CH₂ of (N-1-methylpropyl)) ; 1.50 to 2.20 (mt, 7H : CH₂ at position 15 - CH₂ at position 25 - CH₂ at position 26 and CH at position 29) ; 1.79 (s, 3H : CH₃ at position 33) ; 2.74 (mt, 1H : CH at position 4) ; from 3.00 to 3.10 (mt, 2H : CH of (N-1-methylpropyl) and 1H of CH₂ at position 17) ; 3.25 (dd, J = 16 and 4 Hz, 1H : 1H of CH₂ at position 17) ; from 3.50 to 3.60 (mt, 2H : 1H of CH₂ at position 9 and CH at position 16) ; 3.80 and 3.95 (2 mts, 1H each : CH₂ at position 24) ; 4.28 (mt, 1H : 1H of CH₂ at position 9) ; from 4.70 to 4.85 (mt, 3H : CH at position 3 - CH at position 4 and CH at position 27) ; 5.41 (d, J = 9 Hz, 1H : CH at position 13) ; 5.68 (mt, 1H : CH at position 10) ; 5.80 (d, J = 16 Hz, 1H : CH at position 6) ; from 6.10 to 6.25 (broad unresolved complex, 1H : CONH) ; 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.55 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.11 (s, 1H : CH at position 20).

Example 6

(16R)-16-[(S)-sec-Butylamino]-16-deoxopristinamycin II_B

By carrying out the procedure in a manner similar to that described in Example 1, but starting with 5 g of pristinamycin II_B in solution in 70 cm³ of methanol, 10 g of magnesium sulphate and 1.92 cm³ of (S)-sec-butylamine and by adding after stirring for 20 hours 0.714 g of sodium cyanoborohydride and 5 cm³ of

acetic acid. The reaction mixture is stirred for 2 hours 30 min and gives, after treatment, a solid which is purified by flash chromatography [eluent: dichloromethane-methanol (96-4 by volume)]. The solid
 5 obtained is recrystallized from hot acetonitrile to give 0.590 g of (16R)-16-[(S)-sec-butylamino]-16-deoxopristinamycin II_B in the form of a yellow powder melting at around 150EC (dec.).

10 ¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.09 to 1.15 (mt, 15H : CH₃ at position 30 - CH₃ at position 31 - CH₃ at position 32 and 2 CH₃ of (N-1-methylpropyl)) ; 1.44 (quintuplet, J = 7 Hz, 2H : CH₂ of (N-1-methylpropyl)); 1.60 to 2.00 (mt, 5H : 1H of CH₂ at
 15 position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.76 (s, 3H : CH₃ at position 33) ; 2.04 (broad d, J = 14 Hz, 1H : 1H of CH₂ at position 15) ; 2.11 (mt, 1H : 1H of CH₂ at position 26) ; from 2.65 to 2.85 (mt, 1H : CH at position 4) ;
 20 2.70 and 3.12 (2 dd, respectively J = 16 and 11 Hz and J = 16 and 4 Hz, 1H each : CH₂ at position 17) ; 2.80 (mt, 1H : CH of (N-1-methylpropyl)) ; 3.35 (mt, 1H : CH at position 16) ; 3.50 (mt, 1H : 1H of CH₂ at position 9) ; 3.81 and 3.98 (2 mts, 1H each : CH₂ at position 24)
 25 ; 4.33 (mt, 1H : 1H of CH₂ at position 9) ; from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and CH at position 27) ; 5.43 (d, J = 9 Hz, 1H : CH at position 13) ; 5.62 (mt, 1H : CH at position 10) ; 5.78

(dd, $J = 16$ and 2 Hz, $1H : CH$ at position 6) ; 5.86 (mt, $1H : CONH$) ; 6.17 (d, $J = 16$ Hz, $1H : CH$ at position 11) ; 6.53 (dd, $J = 17$ and 5 Hz, $1H : CH$ at position 5); 8.12 (s, $1H : CH$ at position 20).

5 Example 7

16-Amino-16-deoxopristinamycin II_B

[mixture of the (16R)/(16S) isomers = 75/25]:

200 g of magnesium sulphate, 74 g of ammonium acetate and 28 g of sodium cyanoborohydride are added
10 at about 20EC, under an argon atmosphere, to 100 g of pristinamycin II_B in solution in 1400 cm³ of methanol. After stirring for 20 hours, the reaction mixture is filtered on Celite, and then the Celite rinsed with methanol. The filtrate is concentrated under reduced
15 pressure (2.7 kPa) to give a chestnut-coloured oil which is divided into two equal fractions which are each diluted in 1000 cm³ of dichloromethane and then treated with a 5% aqueous sodium bicarbonate solution. The organic phases are decanted off and the aqueous
20 phases extracted with 1000 cm³ of dichloromethane. The organic phases are combined, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and then concentrated to dryness
25 under reduced pressure (2.7 kPa) to give 97.5 g of a dark yellow powder. The latter is purified by flash chromatography [eluent: dichloromethane-methanol (70-30 by volume)] to give 21.7 g of 16-amino-16-deoxopristinamycin II_B (mixture of the (16R)/(16S)

isomers = 75/25) in the form of a beige-yellow powder.

¹H NMR spectrum [syn (16R) isomer 75% anti (16S) isomer 25%] (400 MHz, CDCl₃, δ in ppm): 0.94 and 0.98 (2d, J = 6.5 Hz : CH₃ at position 30 and CH₃ at position 31 of the syn isomer) ; from 0.90 to 1.15 (mt : CH₃ at position 30 - CH₃ at position 31 and CH₃ at position 32 of the anti isomer) ; 1.07 (d, J = 6.5 Hz : CH₃ at position 32 of the syn isomer) ; 1.46 (mt : 1H of CH₂ at position 15 of the syn isomer) ; from 1.65 to 2.00 (mt : 1H of CH₂ at position 15 of the syn isomer - 1H of CH₂ at position 15 of the anti isomer - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.73 and 1.78 (2 s : respectively CH₃ at position 33 of the anti isomer and CH₃ at position 33 of the syn isomer) ; from 2.00 to 2.30 (mt : 1H of CH₂ at position 15 of the anti isomer and 1H of CH₂ at position 26) ; from 2.65 to 2.80 (mt : CH at position 4 and 1H of CH₂ at position 17 of the syn isomer) ; from 2.80 to 2.90 (mt : CH₂ at position 17 of the anti isomer) ; 2.95 (dd, J = 16 and 5 Hz : 1H of CH₂ at position 17 of the syn isomer) ; from 3.30 to 3.45 (mt : 1H of CH₂ at position 9 of the anti isomer and CH at position 16 of the syn isomer) ; 3.48 (mt : 1H of CH₂ at position 9 of the syn isomer) ; 3.63 (mt : CH at position 16 of the anti isomer) ; 3.80 and 3.91 (2 mts : respectively CH₂ at position 24 of the anti isomer and CH₂ at position 24 of the syn isomer) ; 4.37 (mt : 1H of CH₂ at position 9 of the syn isomer) ;

4.45 (mt : 1H of CH₂ at position 9 of the anti isomer) ;
 from 4.65 to 4.80 (mt : CH at position 3 - CH at
 position 27 and CH at position 14 of the syn isomer) ;
 4.85 (mt : CH at position 14 of the anti isomer) ; 5.40
 5 (d, J = 9 Hz : CH at position 13 of the syn isomer) ;
 5.65 (mt : CH at position 10) ; from 5.70 to 5.85 (mt :
 CH at position 6 and CH at position 13 of the anti
 isomer) ; from 6.00 to 6.15 (mt : CONH) ; 6.18 and 6.22
 (2 d, J = 16 Hz, respectively CH at position 11 of the
 10 syn isomer and CH at position 11 of the anti isomer) ;
 6.45 and 6.52 (2 dd, J = 16 and 5 Hz : respectively CH
 at position 5 of the anti isomer and CH at position 5
 of the syn isomer) ; 8.09 and 8.10 (s : respectively CH
 at position 20 of the syn isomer and CH at position 20
 15 of the anti isomer).

Upon high-performance liquid chromatography
 starting with 16-amino-16-deoxopristinamycin II_B
 (mixture of the (16R)/(16S) isomers = 75/25), (16R)-16-
 amino-16-deoxopristinamycin II_B is obtained in the form
 20 of a white powder melting at around 130EC (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and
 0.99 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and
 CH₃ at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at
 25 position 32) ; 1.45 (mt, 1H : 1H of CH₂ at position
 15) ; from 1.65 to 2.00 (mt, 5H : 1H of CH₂ at position
 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and
 CH at position 29) ; 1.79 (s, 3H : CH₃ at position 33);

2.12 (mt, 1H : 1H of CH₂ at position 26); from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.76 and 2.98 (2¹dd, respectively J = 16 and 8 Hz and J = 16 and 5 Hz, 1H each : CH₂ at position 17) ; 3.42 (mt, 1H : CH at position 16) ; 3.48 (mt, 1H : 1H of CH₂ at position 9); 3.93 (mt, 2H : CH₂ at position 24) ; 4.40 (mt, 1H : 1H of CH₂ at position 9); from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and CH at position 27) ; 5.42 (d, J = 9 Hz, 1H : CH at position 13) ; 5.67 (mt, 1H : CH at position 10) ; 5.79 (dd, J = 17 and 2.5 Hz, 1H : CH at position 6) ; 5.93 (mt, 1H : CONH); 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.12 (s, 1H : CH at position 20).

15 Example 8

16-Methylamino-16-deoxopristinamycin II_B

[mixture of the (16R)/(16S) isomers = 70/30]:

56 g of magnesium sulphate and 9.46 cm³ of methylamine in solution in ethanol (about 8 M) are added at about 20EC, under an argon atmosphere, to 20 g of pristinamycin II_B in solution in 280 cm³ of methanol. The reaction mixture is stirred at about 20EC for 24 hours. The reaction mixture is then filtered on Celite, and then the Celite washed several times with methanol. 2.86 g of sodium cyanoborohydride and 9.46 cm³ of acetic acid are then added to the filtrate. After stirring the reaction mixture for 5 hours, the solution obtained is concentrated to dryness under reduced

pressure (2.7 kPa) at 30EC. The residue is dissolved in 200 cm³ of dichloromethane and then washed with a saturated aqueous sodium bicarbonate solution. The aqueous phases are decanted off and then extracted with 3H100 cm³ of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2.7 kPa) to give 17.8 g of an orange-coloured powder which is purified by flash chromatography [eluent: dichloromethane-methanol (70-30 then 60/40 by volume)]. 10.5 g of 16-methylamino-16-deoxopristinamycin II_B (mixture of the (16R)/(16S) isomers = 70/30 are thus isolated in the form of a yellow powder.

¹H NMR spectrum [syn (16R) isomer 70%, anti (16S) isomer 30%] (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH₃ at position 30 - CH₃ at position 31 and CH₃ at position 32) ; from 1.20 to 1.40 (mt : 1H of CH₂ at position 15 of the syn isomer) ; from 1.65 to 2.00 (mt : 1H of CH₂ at position 15 of the syn isomer - 1H of CH₂ at position 15 of the anti isomer - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.73 and 1.77 (2 s : respectively CH₃ at position 33 of the anti isomer and CH₃ at position 33 of the syn isomer) ; from 2.05 to 2.15 (mt : 1H of CH₂ at position 26) ; 2.18 (dt, J = 15 and 3 Hz, 1H of CH₂ at position 15 of the anti isomer) ; from 2.20 to 2.60 (broad unresolved complex : NH) ; 2.51 and 2.52 (2 s : respectively NCH₃

of the anti isomer and NCH₃ of the syn isomer) ; 2.60 (dd, J = 16 and 11 Hz : 1H of CH₂ at position 17 of the anti isomer) ; from 2.70 to 2.80 (mt : CH at position 4) ; 2.75 (dd, J = 16 and 8 Hz : 1H of CH₂ at position 17 of the syn isomer); from 3.05 to 3.20 (mt : 1H of CH₂ at position 17 and CH at position 16 of the syn isomer) ; from 3.30 to 3.40 (mt : 1H of CH₂ at position 9 of the anti isomer and CH at position 16 of the anti isomer) ; 3.48 (mt : 1H of CH₂ at position 9 of the syn isomer) ; 10 3.83 and 3.98 (2 mts, 2 hours in total : CH₂ at position 24) ; 4.37 (mt : 1H of CH₂ at position 9 of the syn isomer) ; 4.50 (mt : 1H of CH₂ at position 9 of the anti isomer) ; from 4.65 to 4.80 (mt : CH at position 3 - CH at position 27 and CH at position 14 of the syn isomer) 15 ; 4.83 (mt : CH at position 14 of the anti isomer) ; 5.39 (d, J = 9 Hz : CH at position 13 of the syn isomer) ; 5.65 (mt, 1H : CH at position 10) ; from 5.70 to 5.85 (mt : CH at position 6 and CH at position 13 of the anti isomer) ; 5.96 (mt, 1H : CONH) ; 6.16 and 6.23 20 (2 d, J = 16 Hz, 1H in total : respectively CH at position 11 of the syn isomer and CH at position 11 of the anti isomer) ; 6.45 and 6.52 (2 dd, J = 16 and 5 Hz, 1H in total : respectively CH at position 5 of the anti isomer and CH at position 5 of the syn isomer) ; 25 8.10 and 8.12 (s : respectively CH at position 20 of the syn isomer and CH at position 20 of the anti isomer).

Upon high-performance liquid chromatography

starting with 16-methylamino-16-deoxopristinamycin II_B
(mixture of (16R)/(16S) isomers = 70/30), (16R)-16-methylamino-16-deoxopristinamycin II_B is obtained in the form of a yellow solid melting at around 128EC (dec.).

- 5 ¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.96 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.33 (mt, 1H : 1H of CH₂ at position 15) ; from 1.60 to 2.05 (mt, 5H : 1H of CH₂ at position 10 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.75 (s, 3H : CH₃ at position 33) ; 2.11 (mt, 1H : 1H of CH₂ at position 26) ; 2.53 (s, 3H : NCH₃) ; 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.75 and 3.12 (2 dd, respectively J = 16 and 8 Hz and J = 16 15 and 4 Hz, 1H each : CH₂ at position 17) ; 3.10 to 3.20 (mt, 1H : CH at position 16) ; 3.48 (mt, 1H : 1H of CH₂ at position 9) ; 3.82 and 3.98 (2 mts, 1H each : CH₂ at position 24) ; 4.37 (mt, 1H : 1H of CH₂ at position 9) ; from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at 20 position 14 and CH at position 27) ; 5.40 (d, J = 9 Hz, 1H : CH at position 13) ; 5.64 (mt, 1H : CH at position 10) ; 5.78 (dd, J = 17 and 2.5 Hz, 1H : CH at position 6) ; 5.96 (mt, 1H : CONH) ; 6.16 (d, J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd, J = 17 and 5 Hz, 1H : CH at 25 position 5) ; 8.10 (s, 1H : CH at position 20).

Example 9

(16R)-16-Isopropylamino-16-deoxopristinamycin II_B
hydrochloride

72 g of magnesium sulphate, 8.8 g of ammonium acetate and 3.3 g of sodium cyanoborohydride are added at about 20EC, under an argon atmosphere, to 12 g of pristinamycin II_B in solution in 120 cm³ of methanol.

- 5 After stirring for 20 hours, 33.5 cm³ of acetone are added and the reaction mixture is stirred for 7 hours at about 20EC before filtering on Celite. The Celite is washed several times with dichloromethane and the pooled filtrates are concentrated to dryness under
- 10 reduced pressure (2.7 kPa) at 30EC. The residue is dissolved in 400 cm³ of dichloromethane and the solution thus obtained is washed with 3H200 cm³ of a saturated aqueous sodium bicarbonate solution. The final organic phase is concentrated to dryness under reduced pressure
- 15 (2.7 kPa) at 30EC to give 11.3 g of an orange-coloured powder which is purified by flash chromatography [gradient elution: n-butanol-ethyl acetate-ethanol-water (10-60-15-15 then 20-50-15-15 then 30-40-15-15 by volume)] to give 2.92 g of 16-isopropylamino-16-
- 20 deoxopristinamycin II_B (mixture of the (16R)/(16S) isomers = 75/25) in the form of a yellow powder. The two epimers are separated by centrifugal partition chromatography [eluent: ethyl acetate-hexane-methanol-water (2-1-1-1.8 by volume)] to give 0.77 g of (16R)-
- 25 16-isopropylamino-16-deoxopristinamycin II_B in the form of a white powder. The latter is dissolved in a mixture of 10.8 cm³ of 0.1N hydrochloric acid and 27.7 cm³ of water. The solution thus obtained is then filtered and

the filtrate freeze-dried to give 0.72 g of (16R)-16-isopropylamino-16-deoxopristinamycin II_B hydrochloride in the form of a white powder melting at around 135EC (dec.).

5 ¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH₃ at position 30 and CH₃ at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.44 and 1.54 (2 d, J = 6.5 Hz, 3H each : 2 CH₃ of isopropyl) ; from 1.70 to 2.25 (mt, 7H : CH₂ at position 15 - CH₂ at position 25 - CH₂ at position 26 and CH at position 29) ; 1.85 (s, 3H : CH₃ at position 33) ; 2.74 (mt, 1H : CH at position 4) ; 3.34 (mt, 2H : CH₂ at position 17); 3.45 (mt, 1H : CH of isopropyl); 3.56 (mt, 1H : 1H of CH₂ at position 9) ; 3.67 (mt, 1H : CH at position 16) ; 3.82 and 3.95 (2 mts, 1H each : CH₂ at position 24) ; 4.31 (mt, 1H : 1H of CH₂ at position 9) ; from 4.70 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 4.85 (mt, 1H : CH at position 14) ; 5.41 (d, J = 9 Hz, 1H : CH at position 13) ; 5.75 (mt, 1H : CH at position 10) ; 5.83 (dd, J = 16 and 2 Hz, 1H : CH at position 6) ; 6.22 (d, J = 16 Hz, 1H : CH at position 11) ; 6.46 (mt, 1H : CONH) ; 6.54 (dd, J = 16 and 5 Hz, 1H : CH at position 5); 8.10 (s : CH at position 20).

25 Example 10

(16R)-16-Dimethylamino-16-deoxopristinamycin II_B

50 g of magnesium sulphate and 9.5 cm³ of methylamine are added at about 20EC, under an argon

atmosphere, to 20 g of pristinamycin II_B in solution in 300 cm³ of methanol. After stirring for 22 hours, the reaction mixture is cooled to -5EC and 16.1 g of sodium triacetoxymethylborohydride are added. The reaction mixture is stirred for 5 hours between -5EC and 0EC and the temperature is allowed to return to about 20EC over 12 hours. 11.35 g of paraformaldehyde are then added, and then after stirring for 6 hours, 16.1 g of sodium triacetoxymethylborohydride. The mixture is then stirred for 1 hour before adding 2.27 g of paraformaldehyde. After stirring for 16 hours, the reaction mixture is filtered onto Celite. The Celite is washed with 300 cm³ of methanol, the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) to give a residue which is diluted in 500 cm³ of dichloromethane. The organic phase is washed with 600 cm³ of a 5% aqueous sodium bicarbonate solution. The organic phase is decanted off and the aqueous phase is taken up in twice 500 cm³ of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give 23 g of a chestnut-coloured powder which is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (90-5-5 by volume)]. 3.4 g of (16R)-16-dimethylamino-16-deoxopristinamycin II_B are thus obtained in the form of a chestnut-beige powder melting at around 122EC (dec.)

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and

0.98 (2 d, $J = 6.5$ Hz, 3H each : CH_3 at position 30 and CH_3 at position 31) ; 1.07 (d, $J = 6.5$ Hz, 3H : CH_3 at position 32) ; from 1.60 to 2.00 (mt, 6H : CH_2 at position 15 - CH_2 at position 25 - 1H of CH_2 at position 26 and CH at position 29) ; 1.78 (s, 3H : CH_3 at position 33) ; 2.11 (mt, 1H : 1H of CH_2 at position 26) ; 2.36 (s, 6H : $\text{N}(\text{CH}_3)_2$) ; 2.61 (dd, $J = 16$ and 10 Hz, 1H : 1H of CH_2 at position 17) ; 2.72 (mt, 1H : CH at position 4) ; 2.98 (dd, $J = 16$ and 4 Hz, 1H : 1H of CH_2 at position 17) ; 3.21 (mt, 1H : CH at position 16) ; 3.52 (mt, 1H : 1H of CH_2 at position 9) ; 3.83 and 3.92 (2 mts, 1H each : CH_2 at position 24) ; 4.32 (mt, 1H : 1H of CH_2 at position 9) ; 4.67 (mt, 1H : CH at position 14) ; 4.74 (dd, $J = 9$ and 3 Hz, 1H : CH at position 27) ; 4.79 (dd, $J = 10$ and 2 Hz, 1H : CH at position 3) ; 5.35 (d, $J = 9$ Hz, 1H : CH at position 13) ; 5.65 (mt, 1H : CH at position 10) ; 5.78 (dd, $J = 16$ and 2 Hz, 1H : CH at position 6) ; 6.07 (mt, 1H : CONH) ; 6.17 (d, $J = 16$ Hz, 1H : CH at position 11) ; 6.53 (dd, $J = 16$ and 5 Hz, 1H : CH at position 5) ; 8.06 (s : CH at position 20).

Example 11

(16R)-16-(Allyl)(methyl)amino-16-deoxopristinamycin II_B

20 g of magnesium sulphate and 2.3 cm^3 of allylamine are added at around 20EC, under a nitrogen atmosphere, to 7 g of pristinamycin II_B in solution in 100 cm^3 of methanol. After stirring for 21 hours 45 minutes, 0.5 cm^3 of allylamine is added, and then after

4 hours 45 minutes, 1.67 g of sodium cyanoborohydride and then 7 cm³ of acetic acid. The reaction mixture is stirred for 4 hours 30 minutes before adding a further 100 mg of sodium cyanoborohydride. After stirring for a further 25 hours, 2.39 g of paraformaldehyde are added and the stirring is continued. The same quantity of paraformaldehyde is added three times at half-an-hour intervals and one hour after the last addition, 450 mg of sodium cyanoborohydride, 3.5 cm³ of acetic acid and again 2.39 g of paraformaldehyde are added. After stirring for 19 hours 30 minutes, the mixture is filtered on Celite and then rinsed with methanol. The filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30EC and the residue obtained is then taken up in 300 cm³ of methylene chloride and 600 cm³ of a 5% sodium bicarbonate solution. The aqueous phase is decanted off and then extracted with 200 cm³ of methylene chloride. The organic phases are pooled, washed with 300 cm³ of distilled water, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give a solid which is dried under reduced pressure (90 Pa) at 20EC and then purified by flash chromatography [eluent: dichloromethane-methanol (95-5 by volume)]. 1.25 g of (16R)-16-(allyl)(methyl)amino-16-deoxopristinamycin II_B are obtained in the form of an off-white solid melting at around 124EC (dec.).

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and

0.99 (2 d, $J = 6.5$ Hz, 3H each : CH_3 at position 30 and
 CH_3 at position 31) ; 1.08 (d, $J = 6.5$ Hz, 3H : CH_3 at
 position 32) ; from 1.65 to 2.00 (mt, 6H : CH_2 at
 position 15 - CH_2 at position 25 - 1H of CH_2 at position
 5 26 and CH at position 29) ; 1.78 (s, 3H : CH_2 at
 position 33) ; 2.12 (mt, 1H : 1H of CH_2 at position 26) ;
 2.32 (s, 3H : NCH_3) ; 2.64 and 2.98 (2 dd, respectively
 $J = 16$ and 10 Hz and $J = 16$ and 4 Hz, 1H each : CH_2 at
 position 17) ; 2.73 (mt, 1H : CH at position 4) ; 3.05
 10 and 3.28 (2 dd, respectively $J = 14$ and 7 Hz and $J = 14$
 and 6 Hz, 1H each : CH_2 of N(allyl)) ; 3.35 (mt, 1H : CH
 at position 16) ; 3.52 (mt, 1H : 1H of CH_2 at position
 9) ; 3.84 and 3.93 (2 mts, 1H each : CH_2 at position 24) ;
 4.34 (mt, 1H : 1H of CH_2 at position 9) ; 4.67 (mt, 1H :
 15 CH at position 14) ; 4.75 (dd, $J = 9$ and 2.5 Hz, 1H :
 CH at position 27) ; 4.80 (dd, $J = 8$ and 1.5 Hz, 1H :
 CH at position 3) ; 5.19 and 5.23 (respectively d, $J =$
 10 Hz and dd, $J = 18$ and 1.5 Hz, 1H each : $=\text{CH}_2$ of
 allyl) ; 5.36 (d, $J = 9$ Hz, 1H : CH at position 13) ;
 20 5.67 (mt, 1H : CH at position 10) ; 5.80 (dd, $J = 17$
 and 2.5 Hz, 1H : CH at position 6) ; from 5.80 to 5.95
 (mt, 1H : CH= of allyl) ; 6.02 (mt, 1H : CONH) ; 6.18
 (d, $J = 16$ Hz, 1H : CH at position 11) ; 6.53 (dd, $J =$
 17 and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H : CH
 25 at position 20).

Example 12

16-Propyn-2-ylamino-16-deoxopristinamycin II_A

[mixture of the (16R)/(16S) isomers = 65/35]

0.130 cm³ of propargylamine and then 0.053 cm³
5 of acetic acid are added at a temperature close to
20EC, under an argon atmosphere, to 0.5 g of
pristinamycin II_A in solution in 70 cm³ of anhydrous
acetonitrile. The mixture is stirred for 18 hours at a
temperature close to 20EC and then a further 0.13 cm³ of
10 propargylamine is added. The mixture is stirred for
4 hours at a temperature of 20EC and is then
concentrated under reduced pressure (2.7 kPa) at a
temperature close to 30EC until an insoluble material
appears. 0.072 g of sodium cyanoborohydride and then
15 1.2 cm³ of concentrated acetic acid are then added at a
temperature close to 20EC, under an argon atmosphere.
The mixture is stirred for 1 hour 30 minutes at a
temperature close to 20EC. The reaction mixture is
concentrated to dryness under reduced pressure
20 (2.7 kPa). The residue obtained is then taken up in
dichloromethane and the organic phase washed twice with
a saturated aqueous sodium bicarbonate solution. The
aqueous phases are combined and extracted with
dichloromethane. The organic phases are combined, dried
25 over magnesium sulphate, filtered on sintered glass and
then concentrated to dryness under reduced pressure
(2.7 kPa). The residue obtained is purified by
preparative plate chromatography (Merck silica gel

60 F₂₅₄; thickness = 2 mm, 20H20 cm), eluting with a dichloromethane-methanol-acetonitrile (90-5-5 by volume) mixture to give 0.205 g of 16-propyn-2-ylamino-16-deoxopristinamycin II_A (mixture of the (16R)/(16S) isomers = 65/35) in the form of a beige powder.

¹H NMR spectrum [syn (16R) isomer 65% and anti (16S) isomer 35%] (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH₃ at position 30 and CH₃ at position 31 ; from 1.05 to 1.20 (mt, 3H : CH₃ at position 32) ; from 1.50 to 2.10 (mt : CH₂ at position 15 and CH at position 29) ; 1.64 and 1.74 (2 s : respectively CH₃ at position 33 of the anti isomer and CH₃ at position 33 of the syn isomer) ; 2.27 and 2.32 (2 t, J = 2.5 Hz : respectively CH of 2-propynyl of the syn isomer and CH of 2-propynyl of the anti isomer) ; from 2.55 to 2.95 (mt : CH₂ at position 25 - 1H of CH₂ at position 17 - CH at position 16 of the syn isomer and CH at position 4) ; 3.00 (dd, J = 14 and 2.5 Hz : 1H of CH₂ at position 17 of the syn isomer) ; 3.22 (dd, J = 14 and 2.5 Hz : 1H of CH₂ at position 17 of the anti isomer) ; 3.36 (mt : 1H of CH₂ at position 9 of the anti isomer) ; from 3.45 to 3.60 (mt: NCH₂ of 2-propynyl and CH at position 16 of the anti isomer); 3.82 (broad d, J = 18 Hz : 1H of CH₂ at position 9 of the syn isomer) ; from 4.10 to 4.60 (mt : CH₂ at position 24 - 1H of CH₂ at position 9 and CH at position 14 of the syn isomer) ; from 4.75 to 4.85 (mt : CH at position 14 of the anti isomer and CH

at position 13 of the syn isomer) ; from 4.90 to 5.00
 (mt, 1H : CH at position 3) ; from 5.45 to 5.60 (mt :
 CH at position 10 of the anti isomer) ; 5.50 (d, J = 8
 Hz : CH at position 13 of the anti isomer) ; 5.64 (mt :
 5 CH at position 10 of the syn isomer); from 5.80 to 6.10
 (mt : CH at position 6 - CH at position 11 and CH at
 position 26 of the anti isomer) ; 6.13 (t, J = 3 Hz :
 CH at position 26 of the syn isomer) ; 6.53 (dd, J = 16
 and 6 Hz : CH at position 5 of the anti isomer) ; from
 10 6.55 to 6.70 (mt : CONH of the anti isomer) ; 6.61 (dd,
 J = 16 and 7 Hz ; CH at position 5 of the syn isomer) ;
 7.48 (mt : CONH of the syn isomer) ; 7.87 and 8.08 (2 s :
 respectively CH at position 20 of the syn isomer and CH
 at position 20 of the anti isomer).

15 Example 13

16-Allylamino-16-deoxopristinamycin II_A

[mixture of the (16R)/(16S) isomers = 65/35]

0.054 cm³ of acetic acid is added to a
 suspension of 0.5 g of pristinamycin II_A in 15 cm³ of
 20 acetonitrile and 0.143 cm³ of allylamine, kept at a
 temperature close to 20EC. After one hour at a
 temperature close to 20EC, 0.072 g of sodium
 cyanoborohydride and then 1 cm³ of acetic acid are added
 successively. After one hour at a temperature close to
 25 20EC, 7 cm³ of water and 15 cm³ of dichloromethane are
 added to the reaction mixture. The organic phase is
 decanted off and then washed with twice 10 cm³ of a
 saturated sodium bicarbonate solution. The aqueous

phases are extracted with 10 cm³ of dichloromethane. The pooled organic phases are dried over magnesium sulphate, filtered and concentrated under reduced pressure (about 2.7 kPa) at a temperature close to 40EC. A bright yellow foam is thus obtained which is purified by preparative thin-layer chromatography: Merck preparative plates, Kieselgel 60 F₂₅₄, 20H20 cm, thickness 2 mm, deposition in solution in dichloromethane, eluting with a dichloromethane-methanol-acetonitrile (80-10-10 by volume) mixture to give 0.179 g of 16-allylamino-16-deoxopristinamycin II_A (mixture of the (16R)/(16S) isomers=65/35) in the form of a cream-coloured foam.

¹H NMR spectrum [mixture of the (16R)/(16S) isomers = 65/35] (400 MHz, CDCl₃, δ in ppm): from 0.95 to 1.05 (mt, 6H : CH₃ at position 30 and CH₃ at position 31) ; from 1.10 to 1.20 (mt, 3H : CH₃ at position 32) ; 1.64 and 1.71 (2 s, 3H in total : respectively CH₃ at position 33 of the anti isomer and CH₃ at position 33 of the syn isomer) ; from 1.70 to 2.10 (mt, 3H : CH₂ in position 15 and CH in position 29) ; from 2.60 to 2.90 (mt : CH₂ at position 25 - 1H from CH₂ at position 17 - CH at position 16 of the syn isomer and CH at position 4) ; 3.06 (broad d, J = 14 Hz : 1H of CH₂ at position 17 of the syn isomer) ; 3.22 (broad d, J = 15 Hz : 1H of CH₂ at position 17 of the anti isomer) ; from 3.30 to 3.55 (mt : 1H of CH₂ at position 9 of the anti isomer -

NCH₂ of allyl and CH at position 16 of the anti isomer)
 ; 3.85 (broad d, J = 18 Hz : 1H of CH₂ at position 9 of
 the syn isomer) ; from 4.10 to 4.60 (mt : CH₂ at
 position 24 - 1H of CH₂ at position 9 and CH at position
 5 14 of the syn isomer); 4.80 (mt : CH at position 14 of
 the anti isomer) ; 4.87 (broad d, J = 8 Hz : CH at
 position 13 of the syn isomer) ; from 4.90 to 5.00 (mt,
 1H : CH at position 3) ; from 5.15 to 5.30 (mt : =CH₂ of
 allyl) ; from 5.45 to 5.60 (mt : CH at position 10 of
 10 the anti isomer); 5.55 (d, J = 9 Hz : CH at position 13
 of the anti isomer) ; 5.63 (mt : CH at position 10 of
 the syn isomer) ; from 5.85 to 6.10 (mt : CH at
 position 6 - CH at position 11 - CH at position 26 of
 the anti isomer and =CH of allyl) ; 6.14 (broad s : CH
 15 at position 26 of the syn isomer) ; from 6.45 to 6.60
 (mt : CH at position 5 of the anti isomer and CONH of
 the anti isomer) ; 6.62 (dd, J = 16 and 7 Hz : CH at
 position 5 of the syn isomer) ; 7.39 (mt : CONH of the
 syn isomer) ; 7.88 and 8.07 (2 s : respectively CH at
 20 position 20 of the syn isomer and CH at position 20 of
 the anti isomer).

Example 14

(16R)-16-Dimethylamino-16-deoxopristinamycin II_A

6.9 cm³ of methylamine (8 M in ethanol) and
 25 then 1.43 cm³ of acetic acid are added at a temperature
 close to 20EC, under an argon atmosphere, to 28.5 g of
 pristinamycin II_A in solution in 780 cm³ of anhydrous
 acetonitrile. The mixture is stirred for 48 hours at a

temperature close to 20EC and then 3.8 g of sodium cyanoborohydride and 12 cm³ of acetic acid are added under an argon atmosphere. The mixture is stirred for 3 hours at a temperature close to 20EC before a further addition of 11 cm³ of acetic acid. The reaction mixture is again stirred for 7.5 hours at a temperature close to 20EC. 6 g of paraformaldehyde are then added and the mixture is kept stirred for 17 hours at a temperature close to 20EC. The white suspension obtained is filtered and the filtrate is concentrated under reduced pressure (2.7 kPa) at a temperature close to 30EC. The residual thick oil is then taken up in 800 cm³ of ethyl acetate and in 300 cm³ of water. After stirring for about 15 minutes, the pH of the solution obtained is adjusted first to 9 by addition of concentrated sodium hydroxide, and then to 11 by addition of 150 cm³ of 1 N sodium hydroxide. The mixture obtained is stirred for about one hour before a further addition of 50 cm³ of 1 N sodium hydroxide and stirring for a further one hour approximately. The resulting mixture is separated after settling out and the organic phase washed with twice with 100 cm³ of water and then extracted three times with 1 N HCl (1000 cm³, 100 cm³ and 50 cm³ successively). The pooled acidic aqueous phases are extracted with 200 cm³ of ether and then alkalinized to pH 10-11 by addition of 23 cm³ of concentrated sodium hydroxide. The aqueous phase obtained is extracted with twice 300 cm³ of dichloromethane and the organic phases

are combined, washed with 100 cm³ of water, dried over magnesium sulphate, filtered on sintered glass and then concentrated to dryness under reduced pressure (2.7 kPa) at a temperature close to 30EC to give a white solid. The latter is stirred in 200 cm³ of ether and then filtered and dried to constant weight (90 Pa, at about 20EC), to give 20 g of a white powder. The latter is purified by flash chromatography (eluent: dichloromethane-methanol-acetonitrile (92-4-4 then 84-8-8 by volume)) to give 5.2 g of (16R)-16-dimethylamino-16-deoxopristinamycin II_A in the form of a white solid. 4.5 g of this solid are recrystallized from an acetonitrile-water (18 cm³-9 cm³) mixture to give, after draining and drying under reduced pressure (90 Pa, at about 20EC), 3.46 g of a white powder melting at around 212EC.

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH₂ at position 30 and CH₃ at position 31) ; 1.13 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.63 (mt, 1H : 1H of CH₂ at position 15) ; 1.73 (s, 3H : CH₃ at position 33) ; from 1.95 to 2.10 (mt, 2H : 1H of CH₂ at position 15 and CH at position 29) ; 2.36 (s, 6H : N(CH₃)₂) ; from 2.50 to 2.65 (mt, 2H : 1H of CH₂ at position 17 and CH at position 16) ; from 2.65 to 2.75 (mt, 2H : CH at position 4 and 1H of CH₂ at position 25) ; from 2.80 to 2.95 (mt, 1H : 1H of CH₂ at position 25) ; 2.97 (d, J = 11 Hz, 1H : 1H of CH₂ at position 17) ;

3.79 (broad d, $J = 18$ Hz, 1H : 1H of CH_2 at position 9) ;
 4.21 (mt, 1H : 1H of CH_2 at position 24) ; from 4.30 to
 4.50 (mt, 3H : 1H of CH_2 at position 9 - 1H of CH_2 at
 position 24 and CH at position 14) ; 4.79 (d, $J = 9$ Hz,
 5 1H : CH at position 13) ; 4.97 (dd, $J = 10$ and 1.5 Hz,
 1H : CH at position 3) ; 5.64 (mt, 1H : CH at position
 10) ; 5.90 (broad d, $J = 16$ Hz, 1H : CH at position 11) ;
 6.04 (d, $J = 16$ Hz, 1H : CH at position 6) ; 6.13 (t, $J =$
 3 Hz, 1H : CH at position 26) ; 6.62 (dd, $J = 17$ and 5
 10 Hz, 1H : CH at position 5) ; 7.51 (mt, 1H : CONH) ; 7.87
 (s : CH at position 20).

Example 15

(16R)-16-Methylamino-16-deoxopristinamycin II_A

By carrying out the procedure as described in
 15 Examples 12 and 13, starting with pristinamycin II_A,
 (16R)-16-methylamino-16-deoxopristinamycin II_A is
 obtained in the form of a cream-coloured foam melting
 at around 130°C (dec.).

20 ^1H NMR spectrum (400 MHz, CDCl_3 , δ in ppm): from 0.90 to
 1.05 (mt, 6H : CH_3 at position 30 and CH_3 at position
 31) ; 1.12 (d, $J = 6.5$ Hz, 3H : CH_3 at position 32) ;
 1.72 (s, 3H : CH_3 at position 33) ; from 1.80 to 2.10
 (mt, 3H : CH_2 at position 15 and CH at position 29) ;
 25 2.58 (s, 3H : NCH_3) ; from 2.60 to 2.90 (mt, 4H : CH at
 position 4 - 1H of CH_2 at position 17 and CH_2 at
 position 25) ; 3.12 (dd, $J = 14$ and 1.5 Hz, 1H : 1H of
 CH_2 at position 17) ; from 3.35 to 3.45 (mt, 1H : CH at

position 16) ; 3.86 (broad d, $J = 18$ Hz, 1H : 1H of CH₂ at position 9) ; from 4.18 to 4.40 (mt, 3H : 1H of CH₂ at position 9 and CH₂ at position 24) ; 4.55 (mt, 1H : CH at position 14) ; 4.89 (d, $J = 9$ Hz, 1H : CH at position 13) ; 4.93 (dd, $J = 10$ and 1.5 Hz, 1H : CH at position 3) ; 5.62 (mt, 1H : CH at position 10) ; 5.90 (d, $J = 16$ Hz, 1H : CH at position 11) ; 6.01 (d, $J = 16$ Hz, 1H : CH at position 6) ; 6.14 (t, $J = 3$ Hz, 1H : CH at position 26) ; 6.61 (dd, $J = 17$ and 5 Hz, 1H : CH at position 5) ; 7.38 (mt, 1H : CONH) ; 7.90 (s, 1H : CH at position 20).

Example 16

16-Benzylamino-16-deoxopristinamycin II_A

[mixture of the (16R)/(16S) isomers = 50/50]

By carrying out the procedure as described in Examples 12 and 13, starting with pristinamycin II_A, 16-benzylamino-16-deoxopristinamycin II_A [mixture of the (16R)/(16S) isomers = 50/50] is obtained in the form of a white powder.

20

¹H NMR spectrum [syn (16R) isomer 50% and anti (16S) isomer 50%] (400 MHz, CDCl₃, δ in ppm): from 0.95 to 1.05 (mt, 6H : CH₃ at position 30 and CH₃ at position 31) ; from 1.05 to 1.20 (mt, 3H : CH₃ at position 32) ; 1.45 and 1.63 (2 s : respectively CH₃ at position 33 of the anti isomer and CH₃ at position 33 of the syn isomer) ; from 1.50 to 2.15 (mt, the 3H corresponding to: CH₂ at position 15 and CH at position 29) ; from

2.60 to 2.95 (mt : CH₂ at position 25 - 1H of CH₂ at position 17 of the anti isomer - CH₂ at position 17 of the syn isomer and CH at position 4) ; 3.12 (mt : CH at position 16 of the syn isomer) ; 3.29 (broad d, J = 5 15 Hz : 1H of CH₂ at position 17 of the anti isomer) ; 3.35 (mt : 1H of CH₂ at position 9 of the anti isomer) ; 3.47 (mt : CH at position 16 of the anti isomer) ; from 3.80 to 4.10 (mt : 1H of CH₂ at position 9 of the syn isomer and NCH₂ of benzyl) ; from 4.10 to 4.45 (mt : CH₂ 10 at position 24 - 1H of CH₂ at position 9 of the syn isomer and CH at position 14 of the syn isomer) ; 4.54 (mt : 1H of CH₂ at position 9 of the anti isomer) ; from 4.75 to 4.85 (mt : CH at position 14 of the anti isomer and CH at position 13 of the syn isomer) ; from 4.90 to 15 5.00 (mt, 1H : CH at position 3) ; 5.40 (d, J = 8 Hz : CH at position 13 of the anti isomer) ; from 5.45 to 5.65 (mt, 1H : CH at position 10) ; from 5.80 to 6.05 (mt, 2H at position 6 and CH at position 11) ; 6.08 and 6.14 (2 t, J = 3 Hz, 1H in total : respectively CH at 20 position 26 of the anti isomer and CH at position 26 of the syn isomer) ; from 6.45 to 6.55 (mt : CONH of the anti isomer) ; 6.54 (dd, J = 16 and 6 Hz : CH at position 5 of the anti isomer) ; 6.61 (dd, J = 16 and 7 Hz : CH at position 5 of the syn isomer) ; from 7.25 25 to 7.45 (mt : 5H of phenyl and CONH of the syn isomer) ; 7.86 and 8.09 (2 s : respectively CH at position 20 of the syn isomer and CH at position 20 of the anti isomer).

Example 17

(16R)-16-Methoxyamino-16-deoxopristinamycin II_B

10 g of pristinamycin II_B O-methyloxime (70/30 mixture of the Z and E isomers) in solution in 300 cm³ of methanol and 100 cm³ of acetic acid are placed in a round-bottomed flask kept under a nitrogen atmosphere. The mixture is cooled to -70EC before adding 10.3 g of sodium cyanoborohydride. The temperature is allowed risen slowly to about 20EC and the reaction mixture is left unstirred for 48 hours. An argon stream is passed for one hour through the solution kept under an aspirating fume cupboard and then the solvents are evaporated off under reduced pressure (2.7 kPa) at 20EC and the residue is taken up in 200 cm³ of methylene chloride and 100 cm³ of distilled water. The aqueous phase is alkalinized to pH 8 by addition of 30 cm³ of concentrated NaOH and the mixture is stirred for 30 minutes before being transferred into a separating funnel. The organic phase is decanted off and then washed with twice 100 cm³ of distilled water. The organic phase is decanted off, dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2.7 kPa) at 20EC to give a colourless oil which is stirred in diethyl ether; the precipitate obtained is filtered. 9.1 g of a white powder are thus obtained, which powder is purified by flash chromatography (eluent: CH₂Cl₂-MeOH 97-3 by volume). 1.88 g of (16R)-16-methoxyamino-16-deoxopristinamycin

II_B are isolated in the form of a white powder melting at 195EC.

¹H NMR spectrum (600 MHz, CDCl₃, δ in ppm): 0.95 and
 5 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and
 CH₃ at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH₃ at
 position 32) ; from 1.60 to 2.00 (mt, 6H : CH₂ at
 position 15 - CH₂ at position 25 - 1H of CH₂ at position
 26 and CH at position 29) ; 1.80 (s, 3H : CH₃ at
 10 position 33) ; 2.15 (mt, 1H : 1H of CH₂ at position
 26) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ;
 2.76 and 3.24 (2 dd, respectively J = 16 and 8 Hz and J
 = 16 and 4 Hz, 1H each : CH₂ at position 17) ; from 3.45
 to 3.55 (mt, 2H : CH at position 16 and 1H of CH₂ at
 15 position 9) ; 3.60 (s, 3H : OCH₃) ; 3.92 (mt, 2H : CH₂
 at position 24) ; 4.43 (mt, 1H : 1H of CH₂ at position
 9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH
 at position 14 and CH at position 27) ; 5.34 (d, J =
 9 Hz, 1H : CH at position 13) ; 5.70 (mt, 1H : CH at
 20 position 10) ; 5.80 (dd, J = 16 and 2 Hz, 1H : CH at
 position 6) ; 6.14 (mt, 1H : CONH) ; 6.18 (d, J =
 16 Hz, 1H : CH at position 11) ; 6.51 (dd, J = 16 and
 5 Hz, 1H : CH at position 5) ; 8.09 (s, 1H : CH at
 position 20).

25 Pristinamycin II_B O-methyloxime (70/30 mixture
 of the Z and E isomers) may be prepared in the
 following manner:

20 g of pristinamycin II_B in solution in

800 cm³ of anhydrous pyridine are placed in a three-necked flask and 4.2 g of methoxyamine hydrochloride are added. After stirring for 21 hours, the pyridine is evaporated off under reduced pressure (2.7 kPa) at 40EC and then the residue obtained is taken up in 500 cm³ of methylene chloride and 1 litre of distilled water. The organic phase is decanted off, washed with twice 1 litre of distilled water, dried over sodium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40EC to give a residue which is stirred in 300 cm³ of diethyl ether. The precipitate is filtered, dried under reduced pressure (90 Pa) and then purified by flash chromatography (eluent CH₂Cl₂-MeOH 95-5 by volume). 16.9 g of pristinamycin II_B O-methyloxime (70/30 mixture of the Z and E isomers) are thus obtained in the form of a white solid melting at around 198-199EC (dec.) and which is used as it is in subsequent operations.

¹H NMR spectrum (300 MHz, CDCl₃, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH₃ at position 30 - CH₃ at position 31 and CH₃ at position 32) ; 1.73 and 1.74 (2 s, 3H in total : respectively CH₃ at position 33 of the E isomer and CH₃ at position 33 of the Z isomer) ; from 1.75 to 2.35 (mt : CH₂ at position 25 - CH₂ at position 26 - CH at position 29 and 1H of CH₂ at position 15 of the E isomers) ; 2.51 and 2.65 (2 dd, respectively J = 17 and 6 Hz and J = 17 and 5 Hz : CH₂ at position 15 of the Z

isomer) ; from 2.65 to 2.80 (mt, 1H : CH at position
 4) ; 3.00 (dd, $J = 13$ and 6 Hz : 1H of CH₂ at position
 15 of the E isomer) ; 3.22 (d, $J = 6$ Hz : OH of the Z
 isomer) ; from 3.30 to 3.45 (mt, 1H : 1H of CH₂ at
 5 position 9); 3.58 and 3.68 (2 d, $J = 15$ Hz : CH₂ at
 position 17 of the E isomer) ; from 3.65 to 3.80 (mt,
 1H : 1H of CH₂ at position 24) ; 3.62 and 4.04 (2 d, $J =$
 16.5 Hz : CH₂ at position 17 of the Z isomer) ; 3.92 and
 3.94 (2 s, 3H in total : respectively OCH₃ of the Z
 10 isomer and OCH₃ of the E isomer) ; from 3.95 to 4.20
 (mt, 1H : 1H of CH₂ at position 24) ; 4.35 to 4.55 (mt,
 1H : 1H of CH₂ at position 9) ; from 4.60 to 4.80 (mt,
 2H : CH at position 3 and CH at position 27) ; from
 4.80 to 4.90 (mt : CH at position 13 of the E isomer
 15 and CH at position 14 of the Z isomer) ; 5.06 (mt : CH
 at position 14 of the E isomer) ; 5.57 (d, $J = 9$ Hz :
 CH at position 13 of the Z isomer) ; from 5.60 to 5.90
 (mt, 2H : CH at position 10 and CH at position 6) ;
 6.05 and 6.14 (2 d, $J = 16$ Hz, 1H in total :
 20 . respectively CH at position 11 of the E isomer and CH
 at position 11 of the Z isomer) ; 6.28 (mt : CONH of
 the Z isomer) ; 6.47 (d, $J = 16$ and 5 Hz, 1H : CH at
 position 5) ; 7.47 (mt : CONH of the E isomer) ; 7.77
 (s : CH at position 20 of the E isomer) ; 8.08 (s : CH
 25 at position 20 of the Z isomer).

Example 18(16R)-16-Ethoxyamino-16-deoxopristinamycin II_B

By carrying out the procedure as in Example 17, but starting with 1.53 g of pristinamycin II_B

- 5 O-ethyloxime (50/50 mixture of the E and Z isomers) in solution in 45 cm³ of methanol, 15 cm³ of acetic acid and 1.67 g of sodium cyanoborohydride and after 67 hours of reaction, 1.4 g of a white solid are obtained, which solid is purified by flash chromatography (eluent
- 10 CH₂Cl₂-MeOH 97/3 by volume) to give 360 mg of (16R)-16-ethoxyamino-16-deoxopristinamycin II_B in the form of a white solid melting at 205EC.

- ¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.96 and
- 15 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.19 (t, J = 7 Hz, 3H : CH₃ of ethyl) ; from 1.60 to 2.00 (mt, 6 H : CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at
- 20 position 29) ; 1.80 (s, 3H : CH₃ at position 33) ; 2.14 (mt, 1H : 1H of CH₂ at position 26) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.76 and 3.26 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH₂ at position 17) ; from 3.45 to 3.55 (mt, 2H :
- 25 CH at position 16 and 1H of CH₂ at position 9) ; 3.79 (q, J = 7 Hz, 2H : CH₂ of ethyl) ; 3.93 (mt, 2H : CH₂ at position 24) ; 4.43 (mt, 1H : 1H of CH₂ at position 9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH at

position 14 and CH at position 27) ; 5.34 (d, $J = 9$ Hz, 1H : CH at position 13) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd, $J = 16$ and 2 Hz, 1H : CH at position 6) ; 6.13 (mt, 1H : CONH) ; 6.17 (d, $J = 16$ Hz, 1H : CH at position 11); 6.51 (dd, $J = 16$ and 5 Hz, 1H : CH at position 5); 8.08 (s, 1H : CH at position 20).

Pristinamycin II_B O-ethyloxime (70/30 mixture of the Z and E isomers) may be prepared by carrying out the procedure as in Example 17, but starting with 12 g of pristinamycin II_B. 2.44 g of O-ethyl hydroxylamine hydrochloride in 400 cm³ of pyridine. After extraction and stirring in diethyl ether, 11.28 g of pristinamycin II_B O-ethyloxime (70/30 mixture of the Z and E isomers) are obtained in the form of a light yellow solid melting at around 114EC (dec.) and which is used as it is for subsequent operations.

¹H NMR spectrum of the 70/30 mixture of the two Z/E isomers (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH₃ at position 30 - CH₃ at position 31 and CH₃ at position 32) ; from 1.25 to 1.35 (mt, 3H : CH₃ of ethyl) ; 1.70 and 1.75 (2 s, 3H in total : respectively CH₃ at position 33 of the E isomer and CH₃ at position 33 of the Z isomer) ; from 1.75 to 2.35 (mt : CH₂ at position 25 - CH₂ at position 26 - CH at position 29 and 1H of CH₂ at position 15 of the E isomer) ; 2.52 and 2.68 (2 dd, respectively $J = 16.5$ and 6 Hz and $J = 16.5$ and 5 Hz : CH₂ at position 15 of the Z isomer) ; from

2.70 to 2.80 (mt, 1H : CH at position 4) ; 3.02 (dd, J = 13 and 5 Hz : 1H of CH₂ at position 15 of the E isomer) ; 3.25 (d, J = 6 Hz : OH of the Z isomer) ; from 3.30 to 3.45 (mt, 1H : 1H of CH₂ at position 9) ;
5 3.61 and 3.72 (2 d, J = 15 Hz : CH₂ at position 17 of the E isomer) ; from 3.70 to 3.80 (mt, 1H : 1H of CH₂ at position 24) ; 3.63 and 4.07 (2 d, J = 16 Hz : CH₂ at position 17 of the Z isomer) ; from 4.00 to 4.25 (mt, 3H : 1H of CH₂ at position 24 and OCH₂) ; from 4.40 to
10 4.55 (mt, 1H : 1H of CH₂ at position 9) ; from 4.65 to 4.90 (mt : CH at position 27 - CH at position 3 and CH at position 14 of the Z isomer) ; 4.91 (d, J = 9 Hz : CH at position 13 of the E isomer) ; 5.08 (mt : CH at position 14 of the E isomer) ; 5.59 (d, J = 9 Hz : CH
15 at position 13 of the Z isomer) ; from 5.65 to 5.80 (mt, 1H : CH at position 10) ; 5.79 and 5.85 (2 dd, respectively J = 17 and 2 Hz and J = 17 and 1.5 Hz, 1H in total : CH at position 6 of the Z isomer and CH at position 6 of the E isomer) ; 6.06 and 6.15 (2 d, J =
20 16 Hz, 1H in total : respectively CH at position 11 of the E isomer and CH at position 11 of the Z isomer) ; 6.24 (mt : CONH of the Z isomer) ; from 6.40 to 6.55 (mt, 1H : CH at position 5) ; 7.43 (mt : CONH of the E isomer) ; 7.79 (s : CH at position 20 of the E
25 isomer) ; 8.09 (s : CH at position 20 of the Z isomer).

Example 19

(16R)-16-Allyloxyamino-16-deoxopristinamycin II_B

By carrying out the procedure as in Example 17, but starting with 1.46 g of pristinamycin II_B O-allyloxime (65/35 mixture of the Z/E isomers) in solution in 42 cm³ of methanol, 14 cm³ of acetic acid and 1.57 g of sodium cyanoborohydride and after 96 hours of reaction, 1.3 g of a white solid are isolated, which solid is purified by flash chromatography (eluent (CH₂Cl₂-MeOH 97/3 by volume) to give 0.31 g of (16R)-16-allyloxyamino-16-deoxopristinamycin II_B in the form of a white solid melting at 130EC.

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; from 1.60 to 2.05 (mt, 6H : CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.80 (s, 3H : CH₃ at position 33) ; 2.14 (mt, 1H : 1H of CH₂ at position 26) ; 2.24 (broad s, 1H : OH) ; from 2.70 to 2.85 (mt, 1H : CH at position 4) ; 2.77 and 3.27 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH₂ at position 17) ; from 3.45 to 3.55 (mt, 2H : CH at position 16 and 1H of CH₂ at position 9) ; 3.92 (mt, 2H : CH₂ at position 24) ; 4.25 (mt, 2H : CH₂O) ; 4.43 (mt, 1H : 1H of CH₂ at position 9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and

CH at position 27); 5.23 and 5.30 (2 dd, respectively $J = 10$ and 1.5 Hz and $J = 18$ and 1.5 Hz, 1H each : $=CH_2$ of allyl) ; 5.34 (d, $J = 9$ Hz, 1H : CH at position 13) ; 5.60 (unresolved complex, 1H : NH) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd, $J = 16$ and 2 Hz, 1H : CH at position 6) ; 5.95 (mt, 1H : CH of allyl) ; 6.12 (mt, 1H : CONH) ; 6.18 (d, $J = 16$ Hz, 1H : CH at position 11) ; 6.51 (dd, $J = 16$ and 5 Hz, 1H : CH at position 5) ; 8.09 (s, 1H : CH at position 20).

10 Pristinamycin II_B O-allyloxime (65/55 mixture of the Z and E isomers) may be prepared by carrying out the procedure as in Example 17, but starting with 5 g of pristinamycin II_B, 1.14 g of O-allylhydroxylamine hydrochloride in 200 cm³ of pyridine. After extraction and stirring in diethyl ether, 4.2 g of pristinamycin II_B O-allyloxime (65/55 mixture of the Z and E isomers) are obtained in the form of an ochre-coloured solid melting at 102-104°C and which solid is used as it is for subsequent operations.

20

¹H NMR spectrum (300 MHz, CDCl₃, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH₃ at position 30 - CH₃ at position 31 and CH₃ at position 32) ; 1.73 and 1.74 (2 s, 3H in total : respectively CH₃ at position 33 of the E isomer and CH₃ at position 33 of the Z isomer) ; from 1.75 to 2.35 (mt : CH₂ at position 25 - CH₂ at position 26 - CH at position 29 and 1H of CH₂ at position 15 of the E isomer) ; 2.51 and 2.65 (2 dd, respectively $J = 17$ and

6 Hz and $J = 17$ and 5 Hz : CH_2 at position 15 of the Z isomer) ; from 2.65 to 2.80 (mt, 1H : CH at position 4) ; 3.00 (dd, $J = 13$ and 6 Hz : 1H of CH_2 at position 15 of the E isomer) ; 3.22 (d, $J = 6$ Hz : OH of the Z isomer) ; from 3.30 to 3.45 (mt, 1H : 1H of CH_2 at position 9) ; 3.58 and 3.68 (2 d, $J = 15$ Hz : CH_2 at position 17 of the E isomer) ; from 3.65 to 3.80 (mt, 1H : 1H of CH_2 at position 24) ; 3.62 and 4.04 (2 d, $J = 16.5$ Hz : CH_2 at position 17 of the Z isomer) ; 3.92 and 3.94 (2 s, 3H in total : respectively OCH_3 of the Z isomer and OCH_3 of the E isomer) ; from 3.95 to 4.20 (mt, 1H : 1H of CH_2 at position 24) ; from 4.35 to 4.55 (mt, 1H : 1H of CH_2 at position 9) ; from 4.60 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; from 4.80 to 4.90 (mt : CH at position 13 of the E isomer and CH at position 14 of the Z isomer) ; 5.06 (mt : CH at position 14 of the E isomer) ; 5.57 (d, $J = 9$ Hz : CH at position 13 of the Z isomer) ; from 5.60 to 5.90 (mt, 2H : CH at position 10 and CH at position 6) ; 6.05 and 6.14 (2 d, $J = 16$ Hz, 1H in total : respectively CH at position 11 of the E isomer and CH at position 11 of the Z isomer) ; 6.28 (mt : CONH of the Z isomer) ; 6.47 (d, $J = 16$ and 5 Hz, 1H : CH at position 5) ; 7.47 (mt : CONH of the E isomer) ; 7.77 (s : CH at position 20 of the E isomer) ; 8.08 (s : CH at position 20 of the Z isomer).

Example 20

(16R)-16-Propyloxyamino-16-deoxopristinamycin II_B

- By carrying out the procedure as in Example 17, but starting with 1.5 g of pristinamycin II_B
- 5 O-propyloxime (50/50 mixture of the Z and E isomers) in solution in 45 cm³ of methanol, 15 cm³ of acetic acid and 1.61 g of sodium cyanoborohydride and after 50 hours of reaction, 1.4 g of a white solid are isolated, which solid is purified by flash
- 10 chromatography (eluent CH₂Cl₂-MeOH 97/3 by volume) to give 0.31 g of (16R)-16-propyloxyamino-16-deoxopristinamycin II_B in the form of a white solid melting at 135EC.
- 15 ¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.90 to 1.05 (mt, 9H : CH₃ at position 30 - CH₃ at position 31 and CH₃ of propyl) ; 1.08 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; from 1.55 to 1.70 (mt, 3H : 1H of CH₂ at position 15 and central CH₂ of propyl) ; from 1.70 to
- 20 2.00 (mt, 5H : 1H of CH₂ at position 15 - CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 1.80 (s, 3H : CH₃ at position 33) ; 2.14 (mt, 1H : 1H of CH₂ at position 26) ; from 2.20 to 2.35 (broad unresolved complex, 1H : OH) ; from 2.70 to 2.80
- 25 (mt, 1H : CH at position 4) ; 2.75 (dd, J = 16 and 8 Hz, 1H : 1H of CH₂ at position 17) ; 3.27 (dd, J = 16 and 4 Hz, 1H : 1H of CH₂ at position 17) ; from 3.40 to 3.55 (mt, 2H : CH at position 16 and 1H of CH₂ at

position 9) ; 3.69 (t, $J = 6.5$ Hz, 2H : OCH_2) ; from
 3.85 to 4.00 (mt, 2H : CH_2 at position 24) ; 4.43 (mt,
 1H : 1H of CH_2 at position 9) ; from 4.65 to 4.80 (mt,
 3H : CH at position 3 - CH at position 14 and CH at
 5 position 27) ; 5.36 (d, $J = 9$ Hz, 1H : CH at position
 13) ; from 5.40 to 5.60 (broad unresolved complex, 1H :
 NH) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd, $J =$
 16 and 1.5 Hz, 1H : CH at position 6) ; 6.14 (mt, 1H :
 CONH) ; 6.17 (d, $J = 16$ Hz, 1H : CH at position 11) ;
 10 6.51 (dd, $J = 16$ and 5 Hz, 1H : CH at position 5) ;
 8.08 (s, 1H : CH at position 20).

Pristinamycin II_B O-propyloxime (85/15 mixture
 of the Z and E isomers) may be prepared by carrying out
 the procedure as in Example 17, but starting with 4 g
 15 of pristinamycin II_B, 2.6 g of O-propylhydroxylamine
 hydrochloride in 60 cm³ of pyridine. After extraction
 and drying under reduced pressure (2.7 kPa) at 20EC, a
 solid is obtained which is stirred in acetonitrile to
 give, after filtration of the precipitate, 2.75 g of
 20 pristinamycin II_B O-propyloxime (85/15 mixture of the Z
 and E isomers) in the form of a white solid melting at
 130-132EC and which is used as it is for subsequent
 operations.

25 ¹H NMR spectrum (400 MHz, CDCl_3 , δ in ppm): from 0.90 to
 1.10 (mt, 12H : CH_3 at position 30 - CH_3 at position
 31 - CH_3 at position 32 and CH_3 of propyl) ; from 1.60
 to 1.75 (mt, 2H : central CH_2 of propyl) ; 1.75 (s, 3H :

CH₃ at position 33) ; from 1.75 to 2.00 (mt, 4H : CH₂ at position 25 - 1H of CH₂ at position 26 and CH at position 29) ; 2.15 (mt, 1H : 1H of CH₂ at position 26) ; 2.51 and 2.65 (2 dd, respectively J = 17 and 6 Hz and J = 17.5 and 5 Hz, 1H each : CH₂ at position 15) ; 2.74 (mt, 1H : CH at position 4) ; 3.20 (d, J = 6 Hz, 1H : OH) ; 3.38 (mt, 1H : 1H of CH₂ at position 9) ; 3.65 (d, J = 15 Hz, 1H : 1H of CH₂ at position 17) ; 3.74 (mt, 1H : 1H of CH₂ at position 24) ; from 3.95 to 4.10 (mt, 4H : 1H of CH₂ at position 24 - 1H of CH₂ at position 17 and OCH₂) ; 4.43 (mt, 1H : 1H of CH₂ at position 9) ; 4.67 (dd, J = 10 and 3 Hz, 1H : CH at position 27) ; 4.72 (broad d, J = 10 Hz, 1H : CH at position 3) ; 4.83 (mt, 1H : CH at position 14) ; 5.55 (d, J = 9 Hz, 1H : CH at position 13) ; 5.69 (mt, 1H : CH at position 10) ; 5.78 (dd, J = 17 and 1.5 Hz, 1H : CH at position 6) ; 6.13 (d, J = 16 Hz, 1H : CH at position 11) ; 6.26 (mt, 1H : CONH) ; 6.46 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H : CH at position 20).

Example 21

(16R)-16-Methoxyamino-16-deoxopristinamycin II_A

This compound may be obtained by carrying out the procedure as in Example 17, but starting with 3 g of pristinamycin II_A O-methyloxime (65/25 mixture of the Z and E isomers) in solution in 90 cm³ of methanol, 30 cm³ of acetic acid and 3.4 g of sodium cyanoborohydride and after one week of reaction at

about 20EC and one week of reaction at 30-33EC. 3 g of a white solid are thus obtained, which solid is purified by flash chromatography (eluent CH_2Cl_2 -MeOH 97/3 by volume) to give 0.36 g of (16R)-16-methoxyamino-16-deoxopristinamycin II_A in the form of a white solid melting at 150EC.

^1H NMR spectrum (400 MHz, CDCl_3 , δ in ppm): from 0.90 to 1.05 (mt, 6H : CH_3 at position 30 and CH_3 at position 31) ; 1.13 (d, $J = 6.5$ Hz, 3H : CH_3 at position 32) ; 1.59 (broad s, 1H : OH) ; from 1.65 to 1.85 (mt, 2H : CH_2 at position 15) ; 1.73 (s, 3H : CH_3 at position 33) ; 2.03 (mt, 1H : CH at position 29) ; from 2.60 to 2.85 (mt, 2H : CH at position 4 and 1H of CH_2 at position 25) ; 2.64 (dd, $J = 14$ and 11 Hz, 1H : 1H of CH_2 at position 17) ; 2.85 (mt, 1H : 1H of CH_2 at position 25) ; 2.95 (mt, 1H : CH at position 16) ; 3.20 (dd, $J = 14$ and 2.5 Hz, 1H : 1H of CH_2 at position 17) ; 3.60 (s, 3H : OCH_3) ; 3.81 (broad d, $J = 18$ Hz, 1H : 1H of CH_2 at position 9) ; 4.22 (mt, 1H : 1H of CH_2 at position 24) ; from 4.30 to 4.55 (mt, 3H : 1H of CH_2 at position 9 - 1H of CH_2 at position 24 and CH at position 14) ; 4.83 (d, $J = 9$ Hz, 1H : CH at position 13) ; 4.96 (broad d, $J = 10$ Hz, 1H : CH at position 3) ; 5.47 (broad s, 1H : NH) ; 5.65 (mt, 1H : CH at position 10) ; 5.90 (broad d, $J = 16$ Hz, 1H : CH at position 11) ; 6.03 (broad d, $J = 17$ Hz, 1H : CH at position 6) ; 6.14 (t, $J = 3$ Hz, 1H : CH at position 26) ; 6.62 (dd, $J = 17$ and 7 Hz, 1H : CH

at position 5) ; 7.48 (mt, 1H : CONH) ; 7.87 (s, 1H : CH at position 20).

Pristinamycin II_A O-methyloxime (65/35 mixture of the Z and E isomers) may be obtained by carrying out the procedure as in Example 17, but starting with 8 g of pristinamycin II_A and 1.43 g of methoxyamine hydrochloride in 80 cm³ of pyridine. After evaporation of the pyridine under reduced pressure (2.7 kPa) at 45EC, extraction, stirring of the product in 300 cm³ of diethyl ether, filtration and washing with diethyl ether, 7.51 g of pristinamycin II_A O-methyloxime (65/35 mixture of the Z and E isomers) are obtained after drying under reduced pressure (90 Pa) at 40EC in the form of a white solid melting at around 204EC and which is used as it is in subsequent operations.

Example 22

(16R)-16-(1-Pyrrolidinyl)amino-16-deoxopristinamycin II_B

By carrying out the procedure as in Example 17, but starting with 3 g of pristinamycin II_B in solution in 30 cm³ of methanol, 9 g of magnesium sulphate, 1.6 cm³ of triethylamine and 1.4 g of 1-aminopyrrolidine hydrochloride and after having added, after 18 hours of stirring, 0.43 g of sodium cyanoborohydride and 1.5 cm³ of acetic acid, the reaction mixture is stirred for 4 hours and gives after treatment 3.5 g of a yellow powder which is purified by flash chromatography [eluent: dichloromethane-methanol-

acetonitrile (90-5-5 by volume)]. A solid is thus obtained which is stirred in ethyl ether and separated by filtration to give 0.56 g of (16R)-16-(1-pyrrolidinyl)amino-16-deoxopristinamycin II_B in the form of a beige powder melting at around 130EC.

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): 0.95 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH₃ at position 30 and CH₃ at position 31) ; 1.06 (d, J = 6.5 Hz, 3H : CH₃ at position 32) ; 1.53 (mt, 1H : 1H of CH₂ at position 15) ; from 1.70 to 2.20 (mt, 10H : 1H of CH₂ at position 15 - CH₂ at position 25 - CH₂ at position 26 - CH at position 29 and 2 CH₂ of pyrrolidinyl) ; 1.83 (s, 3H : CH₃ at position 33) ; from 2.70 to 2.90 (mt, 6H : CH at position 4 - 1H of CH₂ at position 17 and 2 CH₂N of pyrrolidinyl) ; 3.06 (dd, J = 16 and 4 Hz, 1H : 1H of CH₂ at position 17) ; from 3.40 to 3.50 (mt, 2H : 1H of CH₂ at position 9 and CH at position 16) ; 3.82 and 3.97 (2 mts, 1H each : CH₂ at position 24) ; 4.37 (mt, 1H : 1H of CH₂ at position 9) ; 4.57 (mt, 1H : CH at position 14) ; 4.73 (dd, J = 9 and 3 Hz, 1H : CH at position 27) ; 4.77 (dd, J = 10 and 2 Hz, 1H : CH at position 3) ; 5.41 (d, J = 9 Hz, 1H : CH at position 13) ; 5.68 (mt, 1H : CH at position 10) ; 5.78 (dd, J = 17 and 2 Hz, 1H : CH at position 6) ; 6.01 (mt, 1H : CONH) ; 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.50 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.10 (s, 1H : CH at position 20).

Example 23

(16R)-16-Dimethylamino-16-deoxypristinamycin II_F

0.069 cm³ of methylamine (8 M in ethanol) and then 0.015 cm³ of acetic acid are added at a temperature close to 20EC, under an argon atmosphere, to 0.27 g of pristinamycin II_F in solution in 7 cm³ of anhydrous acetonitrile. The mixture is stirred for 17 hours at a temperature close to 20EC and then 0.038 g of sodium cyanoborohydride and 0.13 cm³ of acetic acid are added under an argon atmosphere. The mixture is stirred for 3 hours at a temperature close to 20EC before a further addition of 0.1 cm³ of acetic acid. The reaction mixture is again stirred for 7 hours at a temperature close to 20EC. 0.9 g of paraformaldehyde is then added and the medium is kept stirred for 17 hours at a temperature close to 20EC. The white suspension obtained is filtered and the filtrate concentrated to dryness under reduced pressure (2.7 kPa) at a temperature close to 30EC. The residual thick oil is then taken up in 15 cm³ of ethyl acetate and in 3 cm³ of water. After stirring for 15 minutes, the pH of the solution obtained is adjusted first to 9 by addition of concentrated sodium hydroxide, and then to 11 by addition of 1.5 cm³ of 1 N sodium hydroxide. The mixture obtained is stirred for about one hour, separated after settling and the organic phase washed with twice 1 cm³ of water and then extracted three times with 1 N hydrochloric acid (10 cm³, 1 cm³ and 0.5 cm³ successively). The pooled acidic

aqueous phases are washed with 3 cm³ of ether and then
alkalinized to pH 10-11 by addition of concentrated
sodium hydroxide. The aqueous phase obtained is
extracted with twice 4 cm³ of dichloromethane and the
5 organic phases are combined, washed with 2 cm³ of water,
dried over magnesium sulphate, filtered on sintered
glass and then concentrated to dryness under reduced
pressure (2.7 kPa) at a temperature close to 30EC to
give a white solid. The latter is stirred in 5 cm³ of
10 ether and then filtered and dried to constant weight
(90 Pa at 20EC) to give 0.17 g of a white powder. The
latter is purified by flash chromatography [eluent:
dichloromethane-methanol-acetonitrile (92-4-4) to give
0.067 g of (16R)-16-dimethylamino-16-deoxypristinamycin
15 II_F in the form of a white solid melting at 132EC.

¹H NMR spectrum (400 MHz, CDCl₃, δ in ppm): from 0.90 to
1.00 (mt, 6H : CH₃ at position 30 and CH₃ of ethyl at
position 29) ; 1.07 (d, J = 6.5 Hz, 3H : CH₃ at position
20 32) ; 1.18 and 1.50 (2 mts, 1H each : CH₂ of ethyl at
position 29) ; from 1.60 to 2.00 (mt, 6H : CH₂ at
position 15 - CH₂ at position 25 - 1H of CH₂ at position
26 and CH at position 29) ; 1.78 (s, 3H : CH₃ at
position 33) ; 2.12 (mt, 1H : 1H of CH₂ at position 26) ;
25 2.37 (s, 6H : N(CH₃)₂) ; 2.62 and 2.99 (2 dd,
respectively J = 16 and 10 Hz and J = 16 and 4 Hz, 1H
each : CH₂ at position 17) ; 2.76 (mt, 1H : CH at
position 4) ; 3.22 (mt, 1H : CH at position 16) ; 3.51

(mt, 1H : 1H of CH₂ at position 9) ; 3.83 and 3.94
 (2 mts, 1H each : CH₂ at position 24) ; 4.35 (mt, 1H :
 1H of CH₂ at position 9) ; 4.67 (mt, 1H : CH at position
 14) ; 4.75 (dd, J = 9 and 2.5 Hz, 1H : CH at position
 5 27) ; 4.91 (dd, J = 9.5 and 1.5 Hz, 1H : CH at position
 3) ; 5.35 (d, J = 9 Hz, 1H : CH at position 13) ; 5.66
 (mt, 1H : CH at position 10) ; 5.80 (dd, J = 16 and
 1.5 Hz, 1H : CH at position 6) ; 6.02 (mt, 1H : CONH) ;
 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.54 (dd,
 10 J = 16 and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H :
 CH at position 20).

Example 24

By carrying out the procedure in a manner
 analogous to the examples above, the following products
 15 are also prepared:

- (16R)-16-(methoxy) (methyl) amino-16-
deoxopristinamycin II_B
- (16R)-16-(methoxy) (methyl) amino-16-
deoxopristinamycin II_A
- 20 - (16R)-16-(ethoxy) (methyl) amino-16-
deoxopristinamycin II_B
- (16R)-16-(ethoxy) (methyl) amino-16-
deoxopristinamycin II_A
- (16R)-16-(methyl) (propoxyl) amino-16-
25 deoxopristinamycin II_B
- (16R)-16-(methyl) (propoxyl) amino-16-
deoxopristinamycin II_A
- (16R)-16-(allyloxy) (methyl) amino-16-

deoxopristinamycin II_B

- (16R)-16-(allyloxy) (methyl) amino-16-

deoxopristinamycin II_A

- (16R)-16-(cyclopropyl) (methyl) amino-16-

5 deoxopristinamycin II_B

- (16R)-16-(cyclopropyl) (methyl) amino-16-

deoxopristinamycin II_A

- (16R)-16-(methyl) (propyn-2-yl) amino-16-

deoxopristinamycin II_B

10 - (16R)-16-(methyl) (propyn-2-yl) amino-16-

deoxopristinamycin II_A

- (16R)-16-(methyl) (1-pyrrolidinyl) amino-16-

deoxopristinamycin II_B

The present invention also relates to the
15 pharmaceutical compositions containing at least one
streptogramin derivative according to the invention, in
the pure state, combined with a group B streptogramin
derivative, where appropriate in salt form, and/or in
the form of a combination with one or more compatible
20 and pharmaceutically acceptable diluents or adjuvants.

The compositions according to the invention
may be used by the oral, parenteral, topical or rectal
route or in the form of aerosols.

As solid compositions for oral
25 administration, tablets, pills, gelatin capsules,
powders or granules may be used. In these compositions,
the active product according to the invention,
generally in the form of a combination, is mixed with

one or more inert diluents or adjuvants, such as sucrose, lactose or starch. These compositions may comprise substances other than diluents, for example a lubricant such as magnesium stearate or a coating intended for a controlled release.

As liquid compositions for oral administration, there may be used solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents such as water or paraffin oil. These compositions may also comprise substances other than diluents, for example wetting, sweetening or flavouring products.

Compositions for parenteral administration may be emulsions or sterile solutions. As solvent or vehicle, there may be used propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, for example ethyl oleate. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents.

Sterilization may be carried out in several ways, for example with the aid of a bacteriological filter, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

Compositions for topical administration may be, for example, creams, ointments, lotions or

aerosols.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active ingredient, excipients such as
5 cocoa butter, semisynthetic glycerides or polyethylene glycols.

The compositions may also be aerosols. For use in the form of liquid aerosols, the compositions may be stable sterile solutions or solid compositions
10 which are dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active ingredient is finely divided and combined with a water-soluble
15 solid diluent or vehicle with a particle size distribution of 30 to 80 μm , for example dextran, mannitol or lactose.

In human therapy, the new streptogramin derivatives according to the invention are particularly
20 useful in the treatment of infections of bacterial origin. The doses depend on the desired effect and the duration of treatment. The doctor will determine the dosage which he judges to be the most appropriate depending on the treatment, depending on the age,
25 weight and degree of infection and other factors specific to the subject to be treated. Generally, the doses are between 1 and 3 g of active product in 2 or 3 doses per day orally for an adult.

The following example illustrates a composition according to the invention.

EXAMPLE

- Tablets containing a dose of 250 mg of active ingredient and having the following composition are prepared according to the usual technique:
- (16R)-16-dimethylamino-16-deoxo-pristinamycin II_A..... 175 mg
 - pristinamycin I_B..... 75 mg
 - 10 - excipient: starch, hydrated silica, dextrin, gelatin, magnesium stearate: qs..... 500 mg